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(54) Title: SUBTYPE-SELECTIVE NMDA RECEPTOR LIGANDS AND THE USE THEREOF

(57) Abstract

The invention relates to subtype-selective NMDA receptor ligands and the use thereof for treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia and surgery, as well as treating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's diseae, Parkinson's disease and Down's syndrome, treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, treating anxiety, psychosis, convulsions, chronic pain, glaucoma, CMV retinitis, urinary incontinence and inducing anesthesia, as well as for enhancing cognition, treating or preventing opiate tolerance, treating or preventing aminoglycoside antibiotic induced hearing loss, and treating opiate withdrawal.

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Subtype-Selective NMDA Receptor Ligands and the Use Thereof

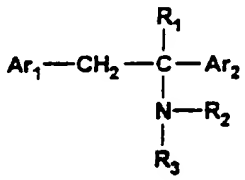
Background of the Invention

Field of the Invention

The invention is in the field of medicinal chemistry. In particular, the invention relates to subtype-selective NMDA receptor ligands and the use thereof to treat or prevent conditions mediated by the excitatory amino acids such as neuronal loss, for example that occurs during ischemia: neurodegenerative conditions such as Parkinson's disease; glaucoma: CMV retinitis, urinary incontinence; convulsions; pain; opiate tolerance, to treat opiate withdrawal; to treat or prevent aminoglycoside-induced hearing loss; and to enhance cognition.

Related Art

U.S. Patent No. 5,430,044 discloses compounds of the Formula (*I*):



(I)

wherein, Ar_1 and Ar_2, which may be the same or different, independently represent phenyl or phenyl substituted by one or more of amino, nitro, halogen, hydroxy, C1 to 6 alkoxy, C1 to 6 alkyl or cyano;

R_1 represents hydrogen, C1 to 6 alkyl, C1 to 6 alkoxy-carbonyl;

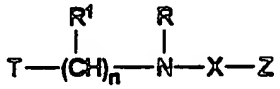
R_2 represents hydrogen or $COCH_2NH_2$;

R_3 represents hydrogen or C1 to 6 alkyl;

in addition, when R_2 represents hydrogen either one or both of Ar_1 and Ar_2 may also represent 2-, 3- or 4-pyridinyl and R_1 may also represent trihalomethyl; or a pharmaceutically acceptable salt thereof.

The compounds having Formula I are reportedly useful for treating neurological disorders such as epilepsy, stroke and cerebral ischemia as well as a number of neurodegenerative diseases.

International Application Publication No. 93/00313 discloses a number of compounds having high binding affinity to the sigma receptor of the Formulae *II, III, IV, V* and *VI*:



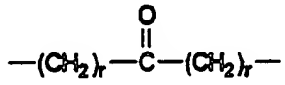
(II)

wherein T is a cycloalkyl group, an optionally substituted aryl group or optionally substituted heteroaryl group, n is 0-5, R is hydrogen or C_1-C_6 alkyl, R^1 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy, amino, C_1-C_6 alkylamino or =O (a double bonded oxygen), or R and R^1 together form a morpholino ring;

X is $-(CH_2)_q-$, wherein q is 1-6;

$-(CH_2)_r-C\equiv C-(CH_2)_r-$, wherein each r is 0-3 independently;

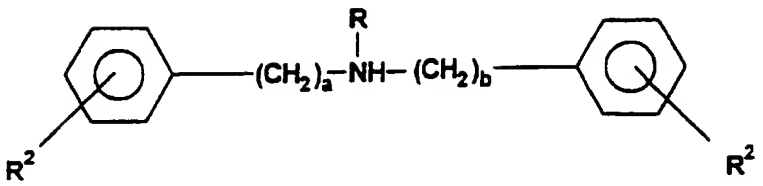
$-(CH_2)_r-CH=CH-(CH_2)_r-$;



$-(CH_2)_r-Y-(CH_2)_r-$, wherein Y is O or S; or

C_1-C_6 alkyl (wherein Z is hydrogen); and

Z is hydrogen, aryl, an aryl-substituted carboxylic acid group, heteroaryl or cycloalkyl, wherein aryl, heteroaryl and cycloalkyl can be optionally substituted;



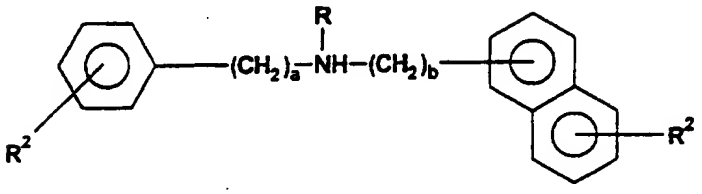
(III)

wherein

a is 1-8;

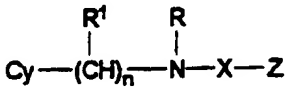
b is 1-8;

R is as defined above;



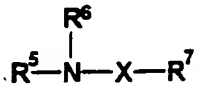
(IV)

wherein R, R^2, a and b, as defined above, may be the same or different;



(V)

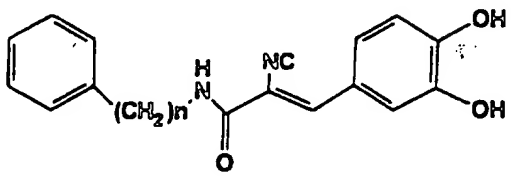
wherein Cy is C_3-C_8 cycloalkyl and Ar, R^1, n, R, X, and Z are defined as above; and



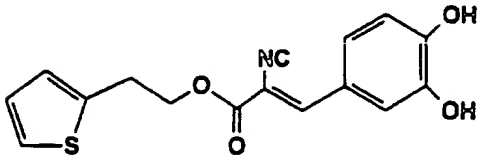
(VI)

wherein R^5 and R^6 are independently a C_{1-8} alkyl group, R^7 is hydrogen or a C_{1-8} alkyl group substituted by an arylacetoxy group, and X is as defined above.

The compounds having Formula *II-VI* are reportedly useful for treating central nervous system disorders, drug abuse, gastrointestinal disorders, hypertension, migraine, angina and depression.



1, 2, 3, n = 2,3,4

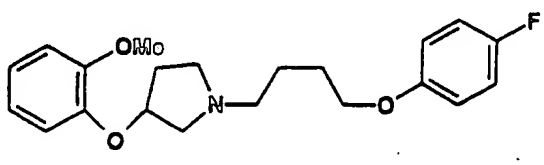


4

Cinnamides 1-3 are reported to be potent EGFR-K inhibitors with high antiproliferative activity (Gazit *et al., J. Med. Chem. 34*:1896 (1991)). Cinnamate 4 is reported to be an extremely potent inhibitor of 12-lipoxygenase (Cho *et al., J. Med. Chem. 34*:1503 (1991)).

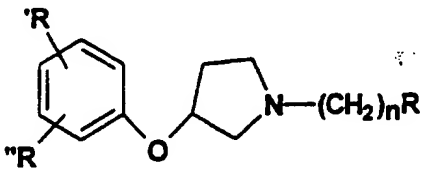
U.S. Patent 5,463,125 discloses that certain phenyl alcohol amides have anticonvulsant activity. Examples of such compounds include 2-hydroxy-2-phenylbutyramide and 3-hydroxy-3-phenylpentamide.

Duncan *et. al., J. Med. Chem. 12*:442-4 (1969) reported the synthesis and biological properties of some 1-substituted 3-(o-methoxyphenoxy)pyrrolidines such as



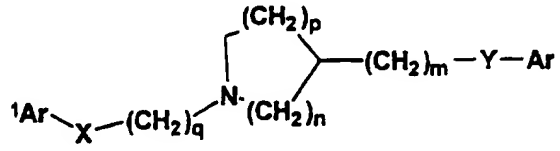
The compounds are said to lower the blood pressure of anesthetized dogs and to generalize central depression in mice.

U.S. 786383 discloses 1-substituted-3-phenoxypyrrolidines described by the formula:



wherein R is C_{1-8} alkyl, alkoxy, alkenyl, or alkynyl, carbamoyl, carbamoyloxy, PhO, BzO, alpha-HO-Bz, styryl, HO, 1,2-diHO-ethyl, amidino, COOalk or Ph. 'R and "R is H, lower alkyl or alkoxy, CF_3, MeCO, F, Cl, or Br, n is 0-4. The compounds are said to be useful as major tranquillisers, anti-convulsants and muscle relaxants. But there is no disclosure or suggestion of treating disorders responsive to selective NMDA receptor subtype antagonists.

European patent application No. 649838 generically disclosed cyclized amines described by the formula:



wherein the nitrogen heterocycles can be 3-8 member rings and substituted in 2-4 positions. Ar and ^{1}Ar are opionally mono or disubstituted phenyl. The compounds are said to be useful to treat arrhythmia and tachycardia. But there is no disclosure or suggestion of treating disorders responsive to selective NMDA receptor subtype antagonists.

In many neurologic disorders, injury to neurons is caused, at least in part, by overstimulation of receptors for the excitatory amino acids, which include

glutamate and aspartate. Such receptors include the N-methyl-D-aspartate (NMDA) ionotropic receptor. Antagonists of the NMDA receptor are considered useful in treating or preventing a number of neurologic disorders which are caused by overstimulation by the excitatory amino acids. These include domoic acid poisoning; cerebral ischemia; stroke; hypoxia; anoxia; poisoning by carbon monoxide, manganese or cyanide; hypoglycemia; mechanical trauma to the nervous system, epileptic seizures; and such chronic neurodegenerative diseases such as Huntington's disease, AIDS dementia, neuropathic pain syndrome, olivopontocerebral atrophy, Parkinson's disease, amyotrophic lateral sclerosis, mitochondrial abnormalities, Alzheimer's disease, hepatic encephalopathy, Tourette's syndrome, and drug addiction. See, *Lipton and Rosenberg, N. Engl. J. Med. 330*:613-622 (1994).

U.S. Patent 5,352,683, discloses the treatment of chronic pain with a compound which is an antagonist of the NMDA receptor.

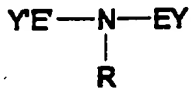
U.S. Patent 4,902,695, discloses certain competitive NMDA antagonists that are useful for the treatment of neurological disorders, including epilepsy, stroke, anxiety, cerebral ischemia, muscular spasms, and neurodegenerative diseases such as Alzheimer's disease and Huntington's disease.

U.S. Patent 5,192,751 discloses a method of treating urinary incontinence in a mammal which comprises administering an effective amount of a competitive NMDA antagonist.

Evidence indicates that the NMDA receptor comprises a class of such receptors with different subunits. Molecular cloning has revealed the existence of at least five subunits of the NMDA receptors designated NR1 & NR2A through 2D. It has been demonstrated that the co-expression of NR1 with one of NR2 subunits forms a receptor with a functional ion channel. (*Ann. Rev. Neurosci. 17*:31-108 (1994)). It is thought that NMDA receptors with different subunit composition generate the different NMDA receptor subtypes found in the mammalian brain.

Summary of the Invention

The invention relates to a subtype-selective NMDA receptor ligand having the Formula (*VII*):



(VII)

wherein

E and E′ are independently $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl (CO), or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

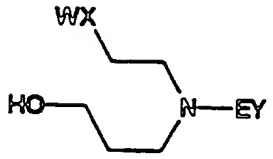
Y and Y′ are independently hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, ≡-Y_1, =-Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino;

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl;

R is hydrogen, alkyl, aryl or aralkyl; and

m is 0, 1, 2, or 3.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*VIII*):



(VIII)

wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, carbonyl (CO), oxygen, or NR;

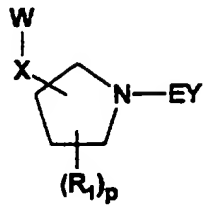
E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, ≡-Y_1, =-Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl; and

R is hydrogen, alkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*IX*):



(IX)

wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, carbonyl, oxygen, sulfur or NR;

E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, =-Y_1, =Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino;

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, optionally substituted cycloalkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

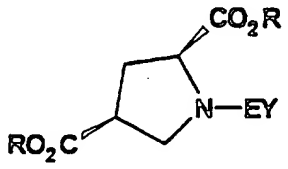
R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, an optionally substituted aryl group, an optionally substituted aralkyl group, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, a heteroaryl group, a heteroaryl substituted alkyl group, a fused cycloalkyl group, a fused cycloalkyl group which is further fused to an optionally substituted benzene ring, a carboxy group or an alkyl carboxy (ester) group;

m is 0, 1, 2, or 3; and

p is 0, 1 or 2.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*X*):



(*X*)

wherein

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, $\equiv Y_1$, $=Y_1$, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino;

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, optionally substituted cycloalkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl

group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

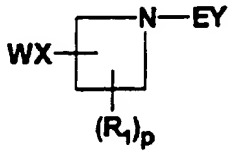
R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, an optionally substituted aryl group, an optionally substituted aralkyl group, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, a heteroaryl group, a heteroaryl substituted alkyl group, a fused cycloalkyl group, a fused cycloalkyl group which is further fused to an optionally substituted benzene ring, a carboxy group or an alkyl carboxy (ester) group;

m is 0, 1 or 2; and

E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XI*):



(XI)

wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, carbonyl, oxygen, or NR;

E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, $\equiv$-Y_1, =-Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino;

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl;

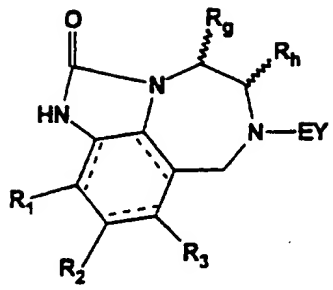
R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

m is 0, 1, 2, or 3; and

p is 0, 1 or 2.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XII*):



(XII)

wherein

R_g and R_h are independently hydrogen or alkyl;

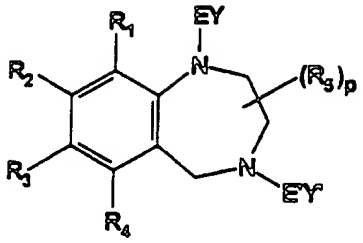
R_1-R_3 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, ≡-Y_1, =-Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl.

The invention relates to a subtype-selective NMDA receptor ligand having the Formula (*XIII*):



(XIII)

wherein

R_1-R_4 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, cyanamido, $N(CN)_2$, guanadino, amidino, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

E and E' are independently $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

R_5 is hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

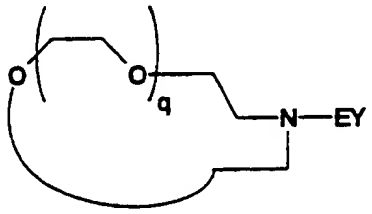
p is 0, 1, 2, or 3;

Y and Y' are independently hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted

arylthioxy, optionally substituted aroyl, ≡-Y_1, =-Y_1 (which may be cis or trans, throughout) carbonylamido, hydrazino, oximo, amidino, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XIV*):



(XIV)

wherein

q is 2, 3, 4 or 5;

E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

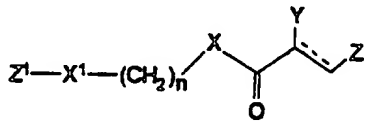
Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, ≡-Y_1, =-Y_1, optionally substituted heterocyclic group,

optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl.

The invention also relates to the quaternary ammonium salts of any one of the compounds above obtained by reacting the compound with a lower alkyl halide, preferable, methyl iodide or methyl sulfate.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XV*):



wherein:

X is NR, O, or CHR^1, wherein R and R^1 are independently hydrogen, alkyl or aralkyl;

X^1 is NR^2, O, S or $(CHR^3)_m$, wherein R^2 and R^3 are independently hydrogen, alkyl or aralkyl and m is 0, 1, 2, 3, 4 or 5;

or where R or R^1 together with R^2 or R^3 is $(CH_2)_p$, wherein p is 0, 1, 2, 3 or 4;

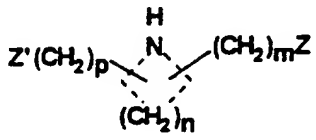
n is 0, 1, 2, 3, 4, 5 or 6;

Z and Z' are independently substituted or unsubstituted aromatic or heteroaromatic groups, adamantyl, hydroxy, or guanidino;

---- can be a single or double bond; and

Y is CN or hydrogen.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XVI*):



wherein:

n is 0, 1, 2, 3, 4 or 5;

m is 0, 1, 2, 3 or 4;

p = 0, 1, 2, 3 or 4; and

Z and Z' are independently substituted or unsubstituted aromatic or heteroaromatic groups, or adamantyl.

The invention also relates to a method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia and surgery, as well as treating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease and Down's syndrome, treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, treating or preventing aminoglycoside antibiotic-induced hearing loss, treating anxiety, convulsions, chronic pain, glaucoma, CMV retinitis, migraine headache and inducing anesthesia, as well as enhancing cognition, treating glaucoma, treating or preventing opiate tolerance, and treating opiate withdrawal, comprising administering to an animal in need of such treatment an effective amount of any one of the subtype-selective NMDA receptor ligands of the present invention, or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

The present invention relates to the discovery of new compounds which are subtype-selective ligands of the NMDA receptor. Such subtype selective ligands will allow for the treatment of various conditions mediated through binding to the NMDA receptor, while minimizing unwanted side effects.

Electrophysiological assays may be utilized to characterize the actions of potential subtype-selective ligands at NMDA receptors expressed in Xenopus oocytes. The ligand may be assayed at the different subunit combinations of cloned rat NMDA receptors corresponding to the four putative NMDA receptor subtypes (*Moriyoshi et al., Nature (Lond.) 354*:31-37 (1991); *Monyer et al., Science (Washington, D.C.) 256*:1217-1221 (1992); *Kutsuwada et al., Nature (Lond.) 358*:36-41 (1992); Sugihara *et al., Biochem. Biophys. Res. Comm. 185*:826-832 (1992)).

Using fixed saturating concentrations of agonists (glutamate 100 mM, glycine 1-10 mM depending on subunit combination), the inhibitory potency of a putative subtype-selective ligand may be assayed at the NMDA receptors assembled from NR1A/2A, NR1A/2B, NR1A/2C and NR1A/2D subunit combinations.

Preferably, the subtype selective NMDA receptor ligands are limited efficacy NMDA receptor antagonists. Such limited efficacy antagonists are attractive because such drugs have built-in safety margins; no matter how high the dosage only a certain fraction of the response can be blocked. This could be particularly important for analgesic, anticonvulsant, anti-psychotic, antimigraine, headache, anti-Parkinson's disease and antiglaucoma indications, where overdosage of full antagonists may result in sedation. It is also likely that low efficacy NMDA receptor antagonists, particularly those showing

subtype-selectivity, will not induce such profound memory deficits as full antagonists.

Certain of the subtype-selective NMDA receptor ligands are expected to be able to mediate either inhibition or potentiation of membrane current response. Which type of effect predominates appears to be dependent upon the subunit composition of the receptors. The 1A/2A and 1A/2B subtypes are mainly in the forebrain. The 1A/2C and 1A/2D are mainly in cerebellum. In addition to the potential of developing subtype selective drugs for the treatment of diseases associated with the overstimulation of the NMDA receptor with fewer side effects. it is also possible to develop drugs that selectively potentiate particular subtypes of NMDA receptors present in particular parts of the brain. Such drugs could show therapeutic potential as cognitive-enhancers in treatments of neurodegenerative conditions such as Alzheimer's disease. Furthermore, there is potential of developing drugs that selectively potentiate some subtypes of NMDA receptor while simultaneously having inhibitory effects at other subtypes. Such compounds could be important for adjusting imbalances in subtype activity and may have therapeutic potential as psychotropic agents.

Compounds which are useful for treating or preventing the adverse consequences of stroke, hypoglycemia, neurodegenerative disorders, anxiety, epilepsy or psychosis, which induce analgesia, or which prevent aminoglycoside antibiotic-induced hearing loss, will inhibit the currents across the membranes of the oocyte expressing various subtype NMDA receptors. However, if the compound potentiates currents across the oocyte membrane, then the compound is expected to be useful in enhancing cognition.

With respect to the formulae, above:

Typical C_{6-14} aryl groups include phenyl, naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl and fluorenyl groups.

Typical halo groups include fluorine, chlorine, bromine and iodine.

Typical C_{1-4} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl, and tert.-butyl groups. Also contemplated is a trimethylene group substituted on two adjoining positions on any benzene ring of the compounds of the invention.

Typical C_{2-4} alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and sec.-butenyl.

Typical C_{2-4} alkynyl groups include ethynyl, propynyl, butynyl, and 2-butynyl groups.

Typical arylalkyl groups include any of the above-mentioned C_{1-4} alkyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Typical arylalkenyl groups include any of the above-mentioned C_{2-4} alkenyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Typical arylalkynyl groups include any of the above-mentioned C_{2-4} alkynyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Typical haloalkyl groups include C_{1-4} alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms, e.g. fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl and trichloromethyl groups.

Typical hydroxyalkyl groups include C_{1-4} alkyl groups substituted by hydroxy, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups.

Typical alkoxy groups include oxygen substituted by one of the C_{1-4} alkyl groups mentioned above.

Typical alkylthio groups include sulphur substituted by one of the C_{1-4} alkyl groups mentioned above.

Typical acylamino groups include any C_{1-6}acyl (alkanoyl) substituted nitrogen, e.g. acetamido, propionamido, butanoylamido, pentanoylamido, hexanoylamido as well as aryl-substituted C_{2-6} substituted acyl groups.

Typical acyloxy groups include any C_{1-6} acyloxy groups, e.g. acetoxy, propionoyloxy. butanoyloxy, pentanoyloxy, hexanoyloxy and the like.

Typical heterocyclic groups include tetrahydrofuranyl, pyranyl, piperidinyl, piperizinyl, pyrrolidinyl, imidazolindinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl and pyrazolinyl groups.

Typical heteroaryl groups include any one of the following which may be optionally substituted with one or more alkyl, halo, or hydroxy groups: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl. chromenyl, xanthenyl, phenoxanthiinyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, 5aH-carbozolyl, carbozolyl, β-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl phenoxazinyl groups, 1,4-dihydroquinoxaline-2,3-dione, 7-amino isocoumarin, pyrido[1,2-a]pyrimidin-4-one, 1,2-benzoisoxazol-3-yl, 4-nitrobenzofurazan, benzimidazolyl, 2-oxindolyl and 2-oxobenzimidazolyl. Where the heteroaryl group contains a nitrogen atom in a ring, such nitrogen atom may be in the form of an N-oxide, e.g. a pyridyl N-oxide, pyrazinyl N-oxide, pyrimidinyl N-oxide and the like.

Typical amino groups include $-NH_2$, $-NHR^{14}$, and $-NR^{14}R^{15}$, wherein R^{14} and R^{15} are C_{1-4} alkyl groups as defined above.

Typical carbonylamido groups are carbonyl groups substituted by $-NH_2$, $-NHR^{14}$, and $-NR^{14}R^{15}$ groups as defined above.

When the group is an amidino or guinidino group, any one of the nitrogen atoms may be substituted independently by hydrogen, alkyl, or aryl groups.

Optional substituents on the aryl, aralkyl, aryloxy, arylthioxy, aroyl, heterocyclic, heterocycloxy, heter aryl, heteroaryloxy, cycloalkyl, and

cycloalkoxy groups listed above include any one of the typical halo, haloalkyl, aryl, fused aryl, heterocyclic, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, and alkylthiol groups mentioned above.

In the compounds having the above formulae, the group E is a linker group between the nitrogen, e.g. pyrrolidine nitrogen, and the terminal group Y. Excluded from such Formula are where two heteroatoms are adjacent to one another such that an unstable compound would be produced. Such adjacent heteroatoms include -O-O-, -O-S-(divalent sulfur), -N-S-(divalent sulfur), -S-O-(divalent sulfur), and -S-N-(divalent sulfur). Hydrazine groups (-N-N-) are contemplated as possible linkers. Preferably, the group E is an optionally substituted methylene linker. Most preferably, the group E is a methylene linker $(CH_2)_n$, wherein n is 1, 2, 3, 4, 5 or 6.

Preferably, the group Y is an N-hydroxyalkyl (e.g., hydroxypropyl) group, which is expected to provide a reduction in affinity to the α_1 receptor, thereby resulting in less hypotension when the compounds are administered to animals. See, Gifford, R.W. *et al., Arch. Intern. Med. 153*:154-183 (1993). Alternatively, a halo group such as a *p*-chlorophenyl group may be employed to give compounds having a prolonged *in vivo* activity.

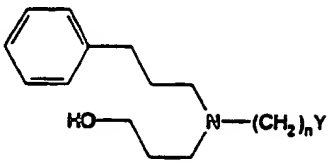
The compounds of the invention may be prepared by reaction of an appropriately substituted amino compound with a suitable electrophile in an aprotic solvent such as toluene or acetonitrile. Optionally, a base such as potassium carbonate or pyridine may be added. Examples of suitable electrophiles include, for example, an alkyl, alkenyl, alkynyl, aralkyl, aryloxyalkyl, or heteroaralkyl halide, sulfate, sulfonate, or isocyanate. Specific examples of such electrophiles include ethyl 3-bromoethoxyphenyl acetate, methyl 5-bromovalerate, ethyl 4-bromobutyrate, 3-butyn-1-methanesulfate, ethyl crotonate, 1-chloro-4-phenylbutane, 3-phenoxypropyl bromide,

4-chloro-4'-fluorobutyrophenone, 4-chlorobutyrophenone, 2-phenylethyl bromide, 1-bromo-3-phenylpropane, 3-phenoxypropyl bromide, β-bromo-phenetole, 3-phenoxypropyl bromide, 3-phenylpropyl bromide, 1,3-propanesulfone, phenylisocyanate, 4-nitrophenylisocyanate, allyl iodide, bromomethylcyclopropane, 3-bromo-1-propanol, and 5-bromovaleronitrile.

A general procedure for reaction of the amino compound with an alkyl chloride, bromide, tosylate or mesylate involves forming a mixture of a free base of the amino compound and an alkyl chloride or bromide in toluene, acetonitrile, DMF, acetone or ethanol, in the presence of NaI. The reaction may be refluxed for 1-10 h then cooled to room temperature. filtered and washed with hexane. The filtrate is evaporated, and the residue chromatographed over silica gel to give the product. If the product is a solid, it may be crystallized, for example, from hexane or hexane-ethyl acetate. If the product is an oil, it may be dissolved in acetone and 4N HCl solution in 1,4-dioxane or concentrated HCl may be added until the mixture becomes strongly acidic (pH < 2). It may then be rota-evaporated, and co-evaporated until a solid residue is obtained. The solid may then be recrystallized from acetone to give the hydrochloride. Alternatively, the hydrobromide or other acid addition salts may be prepared by substitution of, for example, HBr or maleic acid for HCl.

Thus, compounds having Formula VII may be prepared by the reaction of an appropriate amino compound EYNHR with a suitable electrophile XE'Y'. Examples of such compounds include N-(2-phenylethyl)-N-(3-phenylpropyl)amine, N-(1-methyl-2-hydroxy-2-phenylethyl)-N-(3-phenylpropyl)amine, N-(3-phenoxypropyl)-N-(1-phenylcyclohexyl)amine, bis-N,N-(2-(4-fluorophenoxy)ethyl)-N-(2-(4-hydroxyphenyl)ethyl)amine hydrochloride, N-(3-(4-chlorophenyl) propyl)-N-(2-(2-fluorophenoxy)ethyl)-N-(3-hydroxypropyl)amine hydrochloride, N-(3-(4-chlorophenyl)propyl)-N-(2-(4-fluorophenoxy)ethyl)-N-(3-hydroxypropyl)amine hydrochloride, Nylidrin (available from RBI), and Isoxsuprine (Sigma).

Examples of compounds having Formula VIII include those having the Formula (*VIIIa*):



wherein

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, ≡-Y_1, =-Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; and

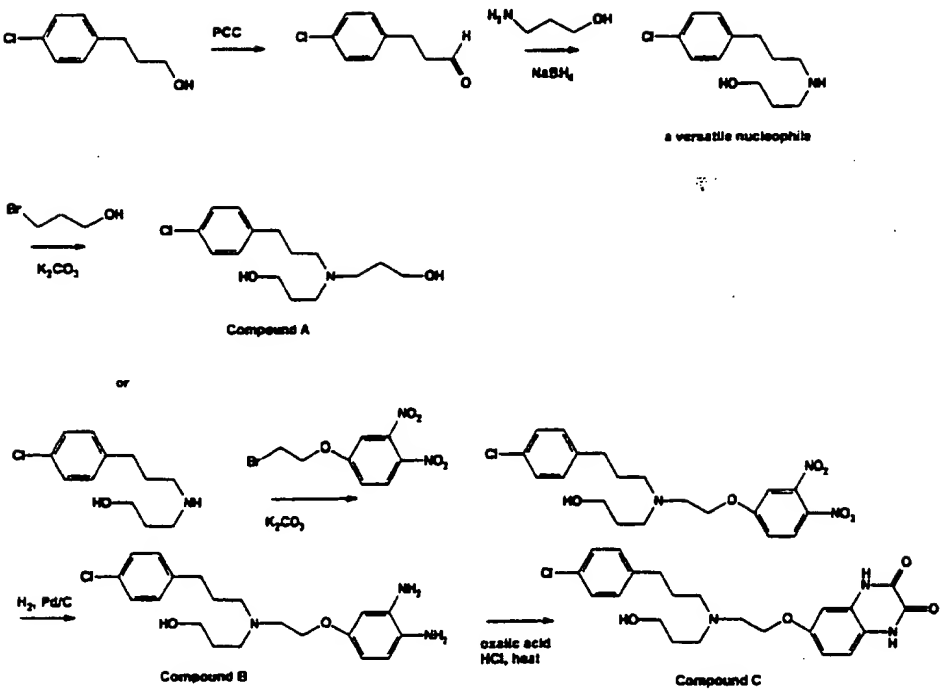
Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl;

R is hydrogen, alkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl; and

n is 0, 1, 2, 3, 4, 5, or 6.

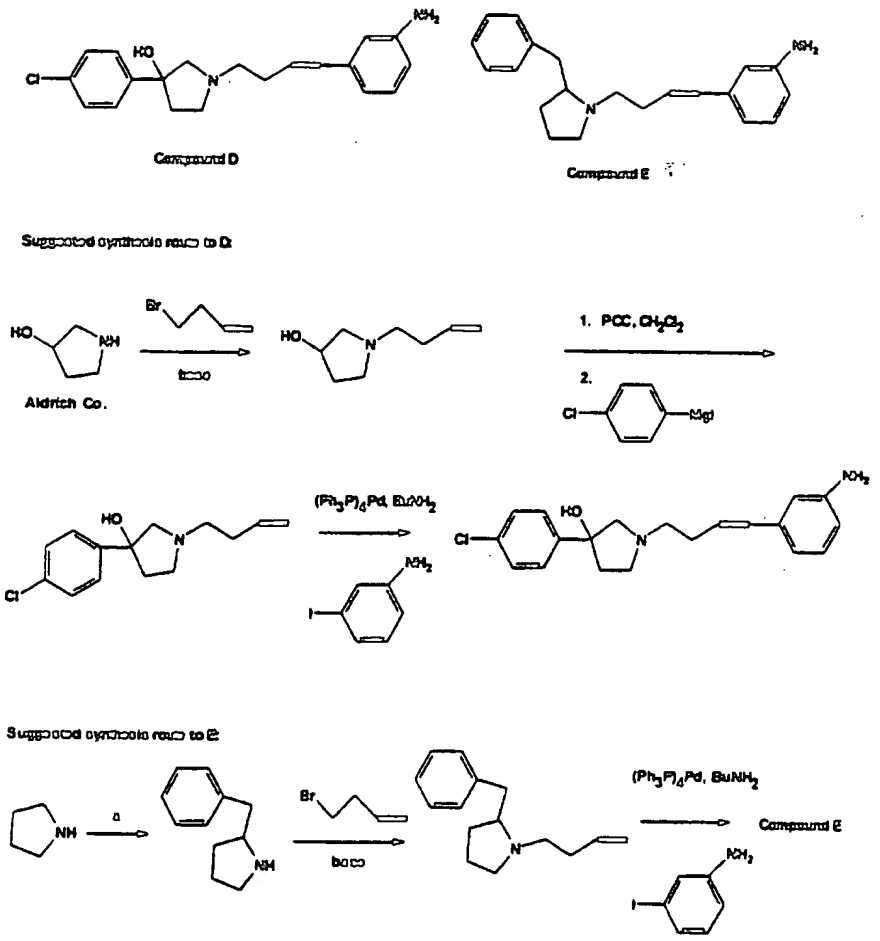
Compounds having Formula *VIIIa* may be prepared, for example, according to Scheme 1:

Scheme 1



Compounds having Formula *IX* may be prepared by reaction of the corresponding pyrrolidine with an electrophile as described above. See Scheme 2 for methods of preparing 2-benzyl pyrrolidines.

Scheme 2



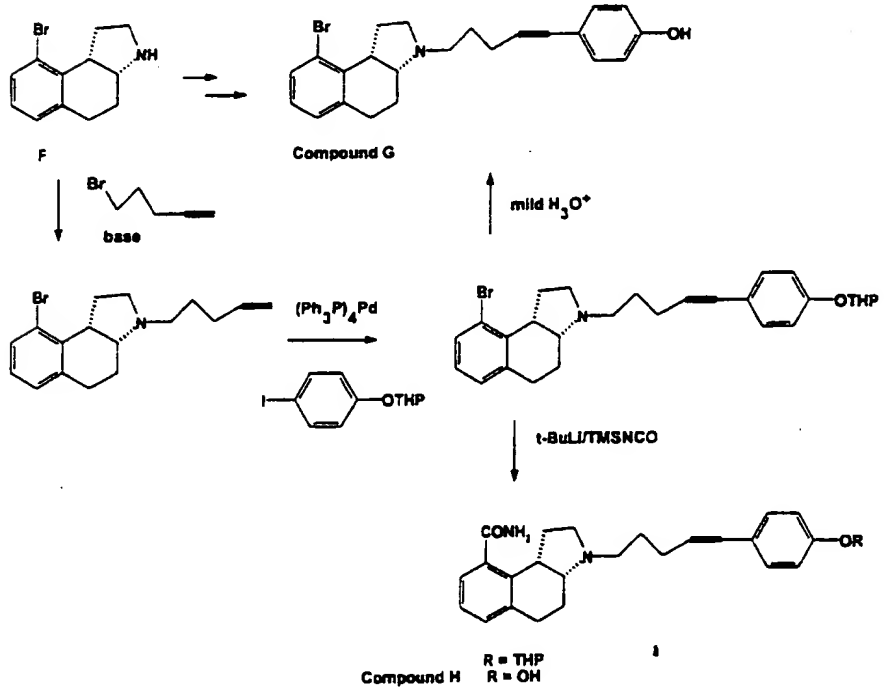
(a) For a review of metalation and electrophilic substitution of amine derivatives adjacent to nitrogen see *Chemical Reviews 84*:471 (1984) and Larock, R. C., *Comprehensive Organic Transformations*, VCH Publishers, New York (1989), pp 402-406; see also Gawley, R. E., Zhang, Q., American Chemical Society, Division of Organic Chemistry, Abstract #173, 209th ACS National Meeting, Anaheim, CA, April, 1995.

This route may be used as a general entry into 2-substituted azetidines and pyrrolidines.

Other pyrrolidines may be used as well. For example, one may use the fused pyrrolidine ring system F described in Haadsma-Svensson, S. R., *et al.*, *J.*

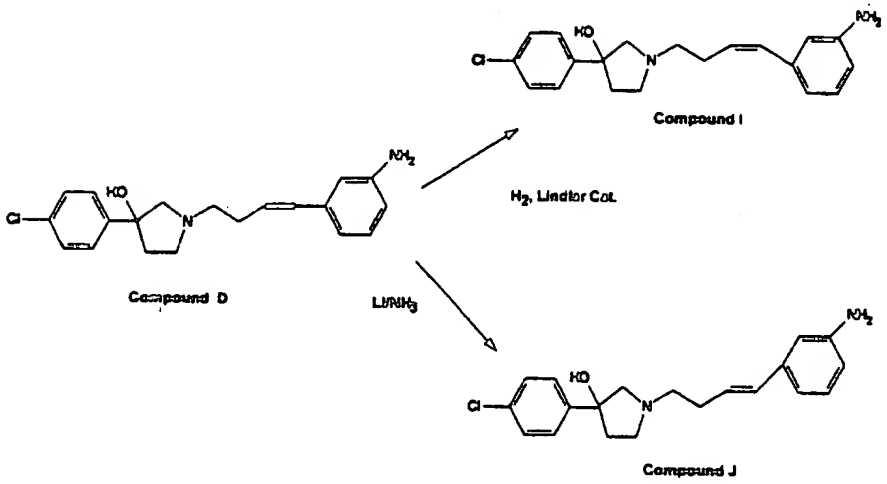
Med. Chem. 38:725 (1995) to prepare a family of subtype selective ligands. A wide variety of electrophilic alkylating agents as described above may be used to alkylate F. One example compound is Compound G, shown below. The bromine atom may then be replaced with a carboxamide group by analogy to work done in the cited paper, giving Compound H.

Scheme 3



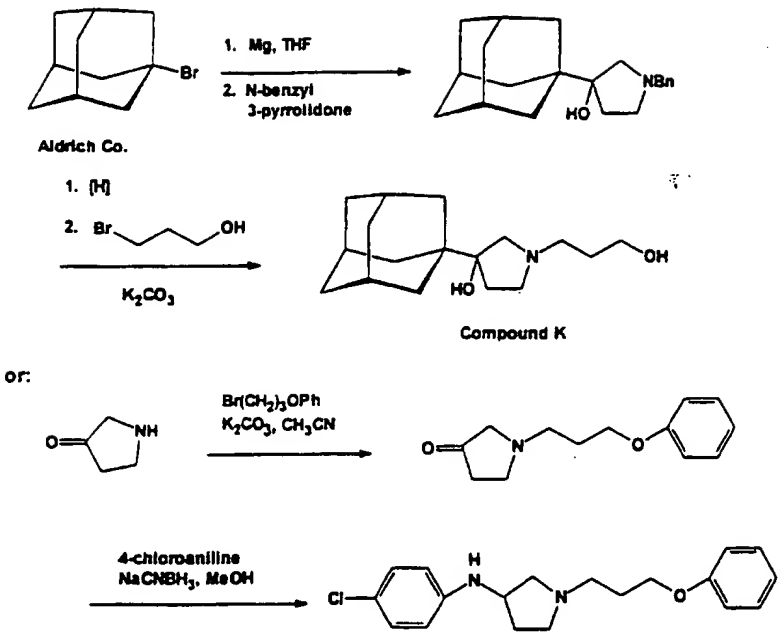
Partially reduced versions of alkynes such as Compound D give the cis (Compound I) or trans (Compound J) alkene. Further catalytic hydrogenation gives the fully reduced hydrocarbon.

Scheme 4



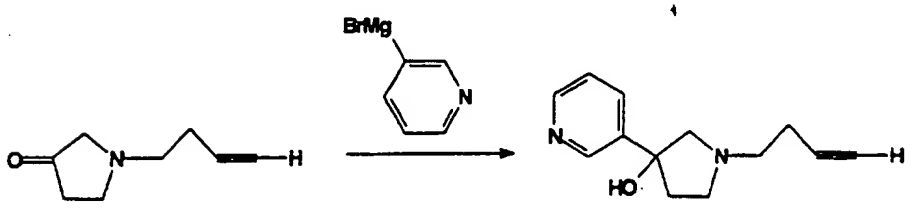
Where W is an adamantyl group, the compounds may be prepared as shown in Scheme 5. Preferably, such adamantyl groups are 1-adamantyl.

Scheme 5



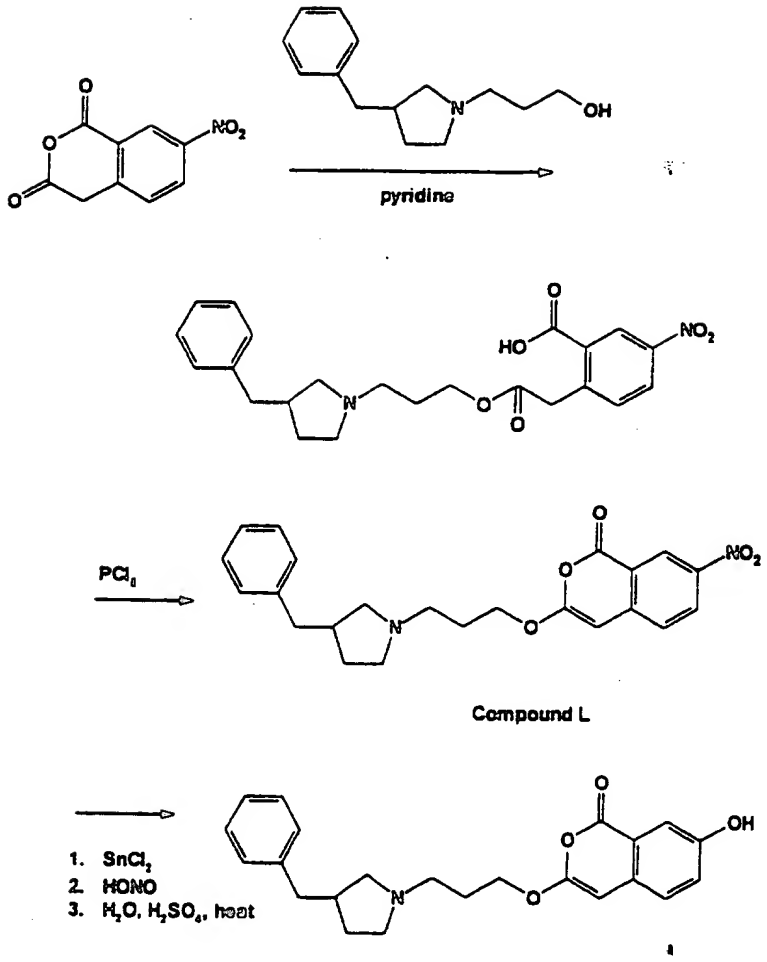
Where W is a heteroaryl group, the compounds may be prepared using an aryl lithium or grignard reagent as shown in Scheme 6.

Scheme 6



Where Y is a 7-substituted isocoumarin, the compounds may be prepared as set forth in Scheme 7.

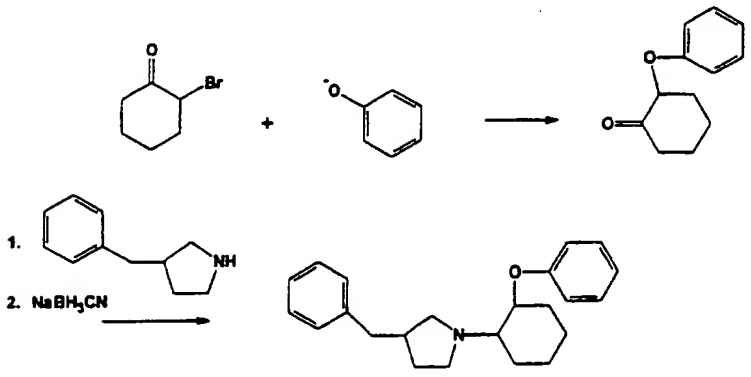
Scheme 7



See, Kerrigan *et al., J. Med. Chem. 38*:544 (1995) for methods of making such 7-substituted isocoumarins wherein the 7-substituent may be an amino group, a nitro group, or amido group.

Where Y is an optionally substituted cycloalkyl group or optionally substituted heterocycloalkyl group, and r, s and t are 0, the compounds may be prepared as shown in Scheme 8.

Scheme 8



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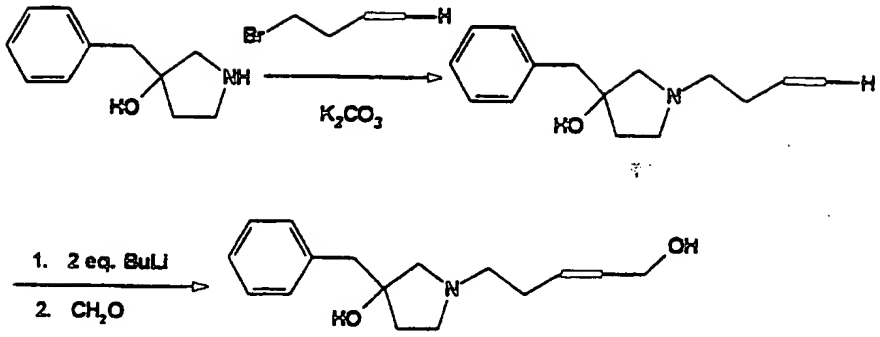
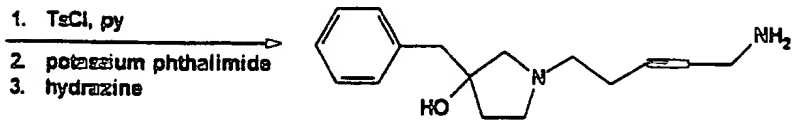
Where the compounds terminate with an alkyne (Y_1 = hydrogen), a propargylalcohol (Y = hydroxyalkyl), or propargylamine (Y_1 = aminoalkyl) residue, they may be prepared according to Scheme 9.

Scheme 9

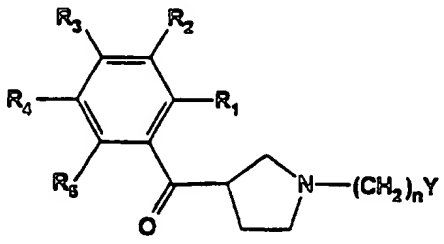


Compound M



Compound N

An example of compounds having Formula *IX* include compounds having the Formula (*IXa*):



wherein

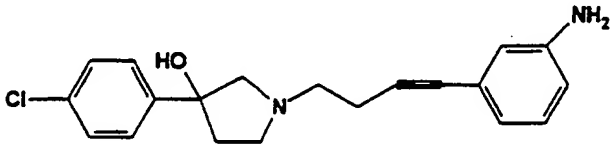
R_1-R_5 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

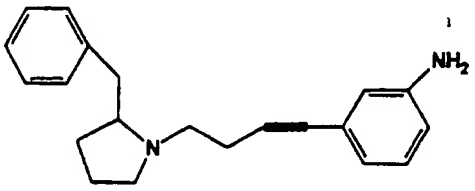
n is 1, 2, 3, 4, 5, or 6;

Y is optionally substituted aryl, optionally substituted aryloxy, SAr, COAr, hydrogen, hydroxy, ≡-Y_1, =-Y_1, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group; and

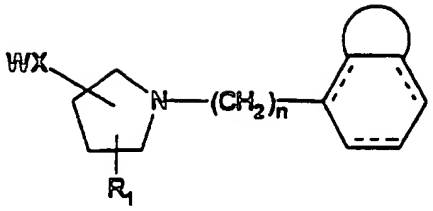
Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group.

Particular examples of compounds having Formula *IX* include:





Another example includes compounds having the Formula (*IXb*):



wherein

W is optionally substituted aryl;

X is a bond, $(CH_2)_m$, oxygen, sulfur, or NR;

R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, aryl, or aralkyl;

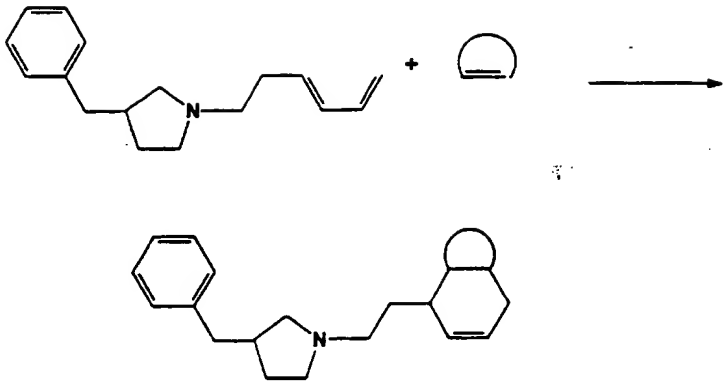
n is 1, 2, 3, 4, 5, or 6;

---- = single or double bond; and

 = carbon ring or heterocyclic ring, with the proviso that said carbon ring is not part of a naphthyl group.

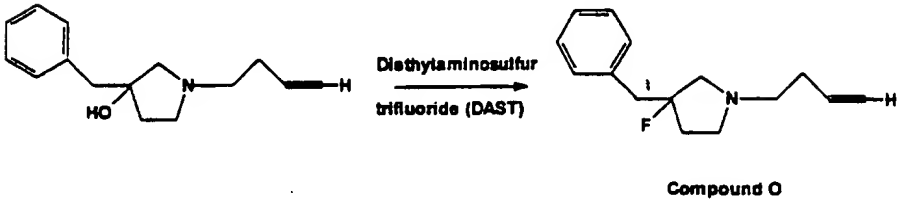
Compounds having Formula *IXb* may be prepared by a Diels-Alder reaction as shown below:

Scheme 10

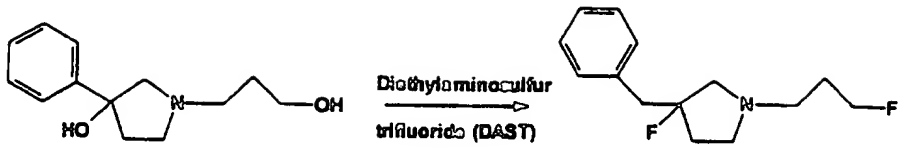


Compounds having Formula *IXc*, where the group R_1 is fluoro, may be prepared by reaction of the corresponding hydroxy pyrrolidine with diethylaminosulfur trifluoride as shown in Scheme 11.

Scheme 11



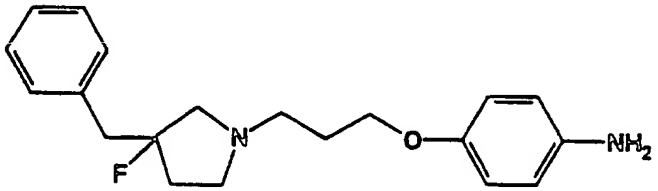
Compound O



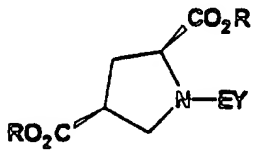
Compound P

See, Sharma, R.A.; Korytnyk, W.; *Tetrahedron Lett 573* (1977); and Fieser, L.F.; Fieser, M., *Reagents for Organic Synthesis 6*:183 (1977).

An example of compounds having Formula *IXc* includes:



The present invention also relates to compounds having the Formula (*X*):



(*X*)

wherein

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, $\equiv$-Y_1, =-Y_1, optionally substituted heterocyclic group,

optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group. optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino;

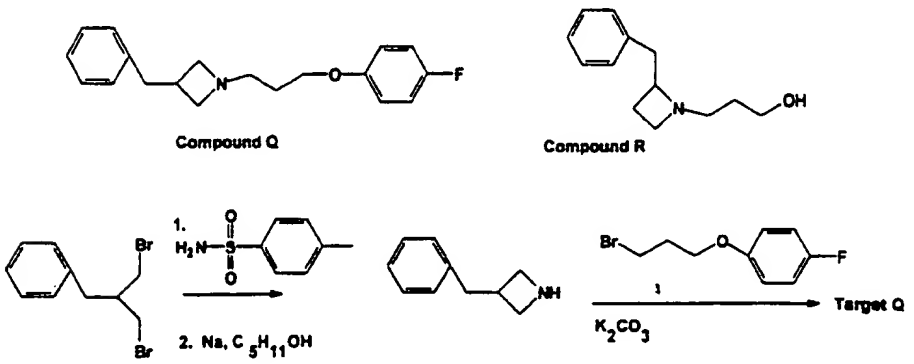
Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl; and

n is 0, 1, 2, 3, 4, 5, or 6; and

each R is a lower alkyl or lower aralkyl group.

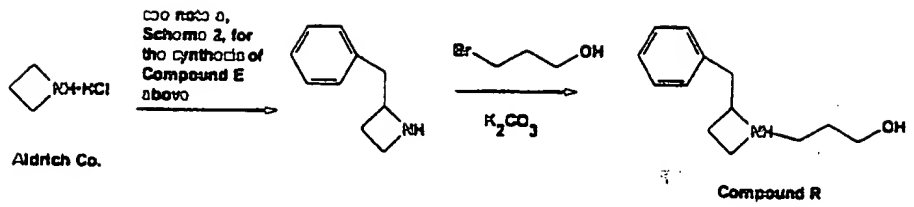
The invention relates as well to azetidine-based compounds having Formula XI in which the A ring is a 2- or 3- or 2,3-(di)substituted azetidine. Compounds Q and R are examples. These compounds may be prepared according to Scheme 12:

Scheme 12

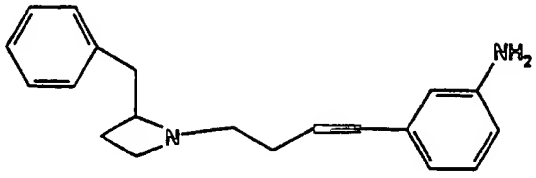


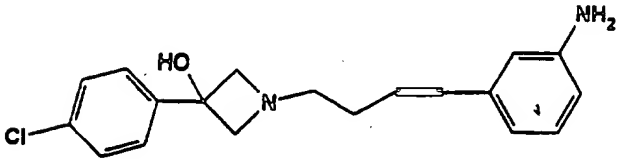
See Acheson, M., Heterocyclic Compounds, Wiley, New York, N.Y. 1960, p. 36. Alternatively, the compounds may be prepared according to the following Scheme 13.

Scheme 13

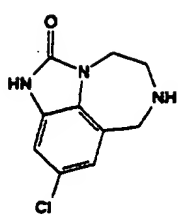
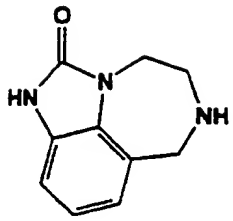
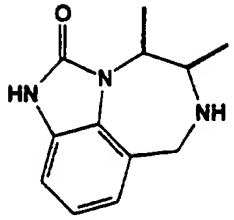
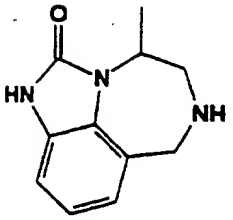


Particular examples of compounds having Formula *XI* include the following:

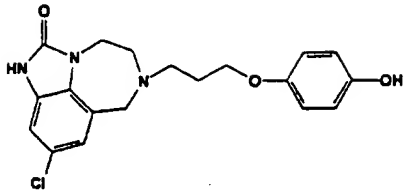




Compounds having Formula *XII* may be prepared by N-alkylation of one of the following benzodiazepine derivatives:

to give, for example, a compound such as:



See, Breslin *et al., J. Med Chem. 38*:771 (1995), for methods of preparing the starting benzodiazepines.

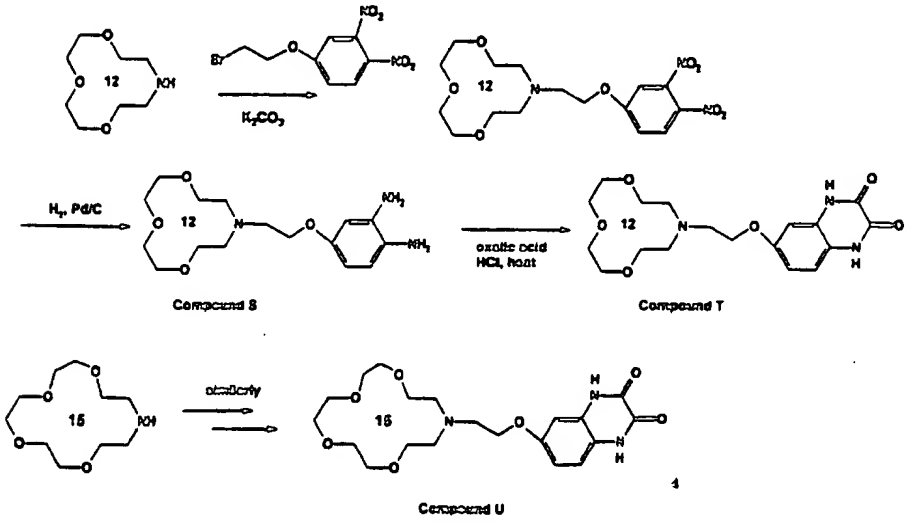
Compounds having Formula ***XIII*** may be prepared by reaction of the corresponding 2-amino substituted anthranilamide with chloroacetyl chloride to give the 1-substituted-3,5(2H,4H)dione-1,4- benzodiazepine. Reduction with lithium aluminum hydride gives the 1-substituted-1H-2,3,4,5-tetrahydro-1,4-

benzodiazepine. Finally, reaction with one of the electrophilic reagents listed above gives the compound having Formula *XIII*.

Examples of compounds having Formula *XIII* include 1-benzyl-4-(3-phenoxypropyl)-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine, 1-benzyl-4-(3-hydroxypropyl)-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine and 1-benzyl-4-(2-phenoxyethyl)-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine.

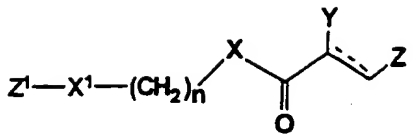
Compounds having Formula *XIV* may be prepared from the aza crown ethers as shown in Scheme 14.

Scheme 14



Examples of such aza crown ethers include 1-aza-12-crown-4, 1-aza-15-crown-5, and 1-aza-18-crown-6.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XV*):



wherein:

X is NR, O, or CHR^1, wherein R and R^1 are independently hydrogen, alkyl or aralkyl;

X^1 is NR^2, O, S or $(CHR^3)_m$, wherein R^2 and R^3 are independently hydrogen, alkyl or aralkyl and m is 0, 1, 2, 3, 4 or 5;

or where R or R^1 together with R^2 or R^3 is $(CH_2)_p$, wherein p is 0, 1, 2, 3 or 4;

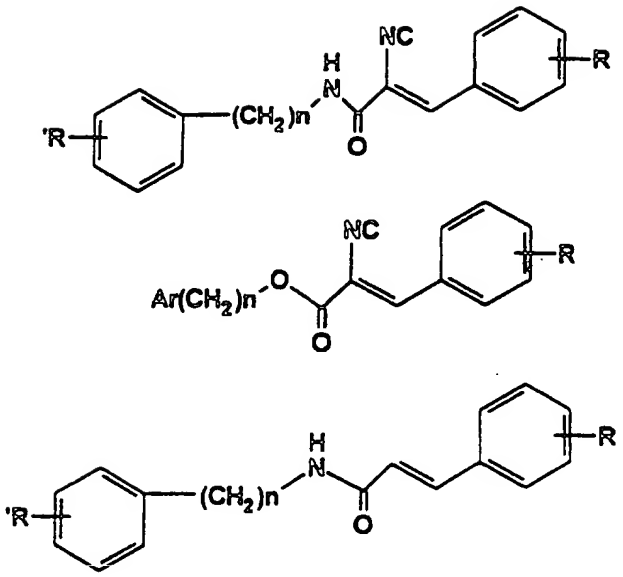
n is 0, 1, 2, 3, 4, 5 or 6;

Z and Z' are independently substituted or unsubstituted aromatic or heteroaromatic groups, adamantyl, hydroxy, or guanidino;

---- can be single or double bond; and

Y is CN or hydrogen.

Particular examples of compounds having Formula XV include:



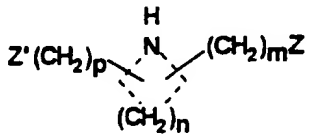
wherein R and R' are independently any one of a number of optional substituents.

Other particular examples include N-(4-phenylbutyl)-3,4-dihydroxycinnamide, N-(4-phenylbutyl)cinnamide, N-(4-phenylbutyl)-4-hydroxycinnamide, 4'-benzylpiperidinyl-4-hydroxycinnamide, N-(4-phenylbutyl)-3-(4-hydroxyphenyl)propionamide, 1,3-bis-(4-hydroxy-benzylidene)acetone, 4-chloro-N-(2-(4-hydroxyphenyl) ethyl)cinnamide, 4-chloro-N-(1-(indol-3-yl)prop-2-yl)cinnamide, 4-chloro-N-(3-phenylpropyl)cinnamide, 4-chloro-N-(3-hydroxypropyl)cinnamide, 2,5-dichloro-N-(4-phenylbutyl)cinnamide, α-cyano-N-(4-phenylbutyl)cinnamide, α-cyano-4-hydroxy-N-(4-phenylbutyl)cinnamide, α-cyano-3-hydroxy-N-(4-phenylbutyl)-cinnamide, α-cyano-4-fluoro-N-(4-phenylbutyl)cinnamide, 4-chloro-α-cyano-N-(4-phenylbutyl)cinnamide, α-cyano-3,4-dihydroxy-N-(4-phenylbutyl)cinnamide, α-cyano-3,4-dihydroxy-N-(3-phenylpropyl)cinnamide, α-cyano-3,4-dihydroxy-N-(2-phenylethyl)cinnamide, and 2-(2-thienyl)ethyl-α-cyano-3,4-dihydroxycinnamate.

The discovery that α-cyano-3,4-dihydroxy-N-(3-phenylpropyl)cinnamide and 2-(2-thienyl)ethyl-α-cyano-3,4-dihydroxycinnamate are subtype selective NMDA receptor antagonists was surprising, as the known subtype selective NMDA receptor antagonists such as ifenprodil and eliprodil all contain a piperidine basic amino group. The cinnamide and cinnamate should have very different chemical and pharmacological properties from the piperidines and should have a completely different side effect profile from that of ifenprodil. For example, the cinnamides have been found to be inactive at α1 receptors.

The discovery that non-cyclized amine such as nylidrin and isoxsuprine are subtype selective NMDA receptor antagonists was also surprising. This demonstrated that the cyclic piperidine structure in the known subtype selective NMDA receptor antagonists such as ifenprodil and eliprodil is not essential for activity.

The invention also relates to compounds having the Formula (*XVI*):



wherein:

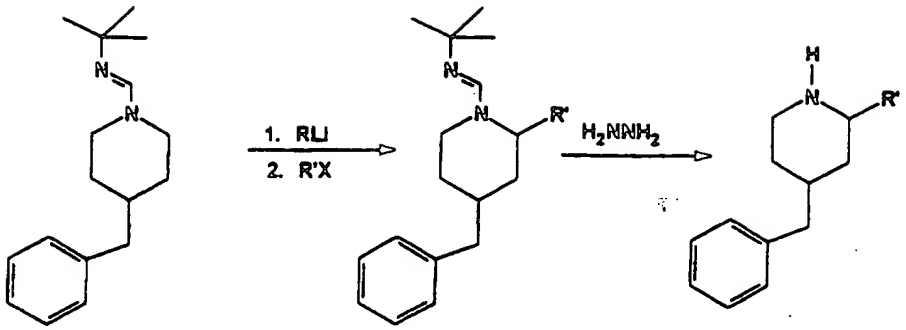
n is 0, 1, 2, 3, 4 or 5;

m is 0, 1, 2, 3 or 4;

p = 0, 1, 2, 3 or 4; and

Z and Z' are independently substituted or unsubstituted aromatic or heteroaromatic groups, or adamantyl.

These compounds can be seen as rigid analogs of the noncyclized amines such as nylidrin and can be prepared using the following chemistry, as shown for the preparation of 2,4-disubstituted piperidines



The compounds of the present invention are active in treating or preventing neuronal loss, neurodegenerative diseases, chronic pain, are active as anticonvulsants and inducing anesthesia. They are also useful for treating epilepsy and psychosis. The therapeutic and side effect profiles of subunit-selective NMDA receptor antagonists and agonists are expected to be markedly different from the more non-selective types of inhibitors. The subtype-selective ligands of the present invention are expected to exhibit little or no untoward side effects caused by non-selective binding with other receptors, particularly, the PCP and glutamate bindings sites associated with the NMDA receptor. In addition, selectivity for different NMDA receptor subtypes is expected to result in reduced side effects such as sedation that are common to non-subtype-selective NMDA receptor antagonists. The compounds of the present invention are effective in treating or preventing the adverse consequences of the hyperactivity of the excitatory amino acids, e.g. those which are involved in the NMDA receptor system, by preventing the ligand-gated cation channels from opening and allowing excessive influx of Ca^{++} into neurons, as occurs during ischemia.

Neurodegenerative diseases which may be treated with the compounds of the present invention include those selected from the group consisting of

Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease and Down's syndrome.

The compounds of the present invention find particular utility in the treatment or prevention of neuronal loss associated with multiple strokes which give rise to dementia. After a patient has been diagnosed as suffering from a stroke, the compounds of the present invention may be administered to ameliorate the immediate ischemia and prevent further neuronal damage that may occur from recurrent strokes.

The compounds of the invention find particular utility in treating or preventing the adverse neurological consequences of surgery. For example, coronary bypass surgery requires the use of heart-lung machines which tend to introduce air bubbles into the circulatory system which may lodge in the brain. The presence of such air bubbles robs neuronal tissue of oxygen, resulting in anoxia and ischemia. Pre- or post- surgical administration of the compounds of the present invention will treat or prevent the resulting ischemia. In a preferred embodiment, the compounds of the invention are administered to patients undergoing cardiopulmonary bypass surgery or carotid endarterectomy surgery.

The compounds of the present invention also find utility in treating or preventing chronic pain. Such chronic pain may be the result of surgery, trauma, headache, arthritis, pain from terminal cancer or degenerative diseases. The compounds of the present invention also find particular utility in the treatment of phantom pain that results from amputation of an extremity. In addition to treatment of pain, the compounds of the invention are also expected to be useful in inducing anesthesia, either general or local anesthesia, for example, during surgery.

Aminoglycoside antibiotics have been used successfully in the treatment of serious Gram-negative bacterial infections. However, prolonged treatment with these antibiotics will result in the destruction of sensory hair cells of the inner ear and consequently, permanent loss of hearing. A recent study of Basile

et al., *Nature Medicine* 2:1338-1343 (1996) indicates that aminoglycosides produce a polyamine-like enhancement of glutamate excitotoxicity through interaction with the NMDA receptor. Thus, the compounds of the present invention with NMDA receptor antagonist activity will be useful in preventing aminoglycoside antibiotic-induced hearing loss by antagonizing their interaction with the receptor.

The subtype-selective NMDA receptor antagonists, agonists and modulators may be tested for *in vivo* anticonvulsant activity after iv or ip injection using a number of anticonvulsant tests in mice (audiogenic seizure model in DBA-2 mice, pentylenetetrazol-induced seizures in mice, maximum electroshock seizure test (MES) or NMDA-induced death). The compounds may also be tested in drug discrimination tests in rats trained to discriminate PCP from saline. It is expected that most of the compounds of the present invention will not generalize to PCP at any dose. In addition, it is also expected that none of the compounds will produce a behavioral excitation in locomotor activity tests in the mouse. It is expected that such results will suggest that the subtype-selective NMDA receptor antagonists and agonists of the present invention do not show the PCP-like behavioral side effects that are common to NMDA channel blockers such as MK-801 and PCP or to competitive NMDA antagonists such as CGS 19755.

Elevated levels of glutamate have been associated with glaucoma. In addition, it has been disclosed that glaucoma management, particularly protection of retinal ganglion cells, can be achieved by administering to a patient a compound capable of reducing glutamate-induced excitotoxicity in a concentration effective to reduce the excitotoxicity. See WO94/13275. Thus, the compounds of the present invention, which are expected to cross the blood-retina barrier, are also expected to be useful in the treatment of glaucoma. Preferably, the invention is directed to the treatment of patients which have primary open-angle glaucoma, chronic closed-angle glaucoma, pseudoexfoliation, or other

types of glaucoma or ocular hypertension. Preferably, the compound is administered over an extended period (e.g. at least six months and preferably at least one year), regardless of the changes in the patient's intraocular pressure over the period of administration.

The compounds of the present invention are also useful in treating CMV retinitis, particularly in combination with antiviral agents. CMV afflicts the ganglion cell layer which may result in higher levels of glutamate. Thus, NMDA receptor antagonists could block retinitis by blocking the toxicity effect of high levels of glutamate.

It is well known to use opiates, e.g., morphine, in the medical field to alleviate pain. (As used herein, the term "opiates" is intended to mean any preparation or derivative of opium, especially the alkaloids naturally contained therein, of which there are about twenty, e.g., morphine, noscapine, codeine, papaverine, and thebaine, and their derivatives.) Unfortunately, with continued use, the body builds up a tolerance for the opiate, and, thus, for continued relief, the patient must be subjected to progressively larger doses. Tolerance develops after both acute and chronic morphine administration (Kornetsky *et al., Science 162*:1011-1012 (1968); Way *et al., J. Pharmacol. Exp Ther. 167*:1-8 (1969); Huidobro *et al., J. Pharmacol. Exp Ther. 198*:318-329 (1976); Lutfy *et al., J. Pharmacol. Exp Ther. 256*:575-580 (1991)). This, in itself, can be detrimental to the patient's health. Furthermore, a time can come when the tolerance is substantially complete and the pain killing properties of the drug are no longer effective. Additionally, administration of higher doses of morphine may lead to respiratory depression, causing the patient to stop breathing. Seeking alternative drugs to produce analgesia without development of tolerance or as an adjunct therapy to block tolerance without interference with analgesia is an active area of research.

Recent studies have suggested a modulatory role for the NMDA receptor in morphine tolerance. (Trujillo *et al., Science 251*:85-87 (1991); Marek *et al.,*

Brain Res. *547*:77-81 (1991); Tiseo *et al.*, *J. Pharmacol. Exp Ther.* *264*:1090-1096 (1993); Lutfy *et al.*, *Brain Res.* *616*:83-88 (1993); Herman *et al.*, *Neuropsychopharmacology* *12*:269-294 (1995)). Further, it has been reported that NMDA receptor antagonists are useful for inhibiting opioid tolerance and some of the symptoms of opioid withdrawal. Thus, the present invention is also directed to the administration of the compounds described herein to inhibit opiate tolerance and to treat or ameliorate the symptoms of opiate withdrawal by blocking the glycine co-agonist site associated with the NMDA receptor.

The compounds of the present invention are also expected to show potent activity *in vivo* after intraperitoneal injection suggesting that these compounds can penetrate the blood/brain barrier and are systemically bioavailable.

Thus, the present invention is directed to compounds having preferred binding to a particular subtype NMDA receptor and, low binding to other sites such as dopamine and other catecholamine receptors, and σ sites. According to the present invention, those compounds having preferred binding to a particular NMDA subtype exhibit an IC_{50} of about 100 μM or less in an NMDA subunit binding assay (see the Examples). Preferably, the compounds of the present invention exhibit an IC_{50} of 10 μM or less. Most preferably, the compounds of the present invention exhibit an IC_{50} of about 1.0 μM or less.

The efficacy of the NMDA subtype selective antagonists to inhibit glutamate neurotoxicity in rat brain cortex neuron cell culture system may be determined according to Choi, D.W., *J. Neuroscience* *7*:357 (1987).

The anticonvulsant activity of the antagonists may be assessed in the audiogenic seizure model in DBA-2 mice as follows. DBA-2 mice may be obtained from Jackson Laboratories, Bar Harbor, Maine. These mice at an age of <27 days develop a tonic seizure within 5-10 seconds and die when they are exposed to a sound of 14 kHz (sinus wave) at 110 dB (Lonsdale, D., *Dev. Pharmacol. Ther.* *4*:28 (1982)). Seizure protection is defined when animals injected with drug 30 minutes prior to sound exposure do not develop a seizure

and do not die during a 1 minute exposure to the sound. 21 day old DBA-2 mice are used for all experiments. Compounds are given intraperitoneally in either saline, DMSO or polyethyleneglycol-400. Appropriate solvent controls are included in each experiment. Dose response curves are constructed by giving increasing doses of drug from 1 mg/kg to 100 mg/kg. Each dose group (or solvent control) consists of at least six animals.

Alternatively, the anticonvulsant activity of the antagonists may be evaluated in the Maximal Electroshock-induced Seizure (MES) test. Seizures are induced by application of current (50 mA, 60 pulses/sec, 0.8 sec pulse width, 1 sec duration, d.c.) through saline-coated corneal electrodes using a Ugo Basile ECT device (Model 7801). Mice are restrained by gripping the loose skin on their dorsal surface, electrodes were held lightly against the two cornea, then current was applied and mice were observed for a period of up to 30 sec for the occurrence of a tonic hindlimb extensor response. A tonic seizure is defined as a hindlimb extension in excess of 90 degrees from the plane of the body. Results are treated in a quantal manner.

The anticonvulsant efficacy of the antagonists may also be assessed in the pentylenetetrazol (PTZ)-induced seizure test according to WO94/00124 and U.S. 5,514,680.

The efficacy of NMDA antagonists to protect mice from NMDA-induced death may be assessed according to WO94/00124 and U.S. 5,514,680.

A series of different evaluations may be conducted on doses of the NMDA antagonists of the invention to determine the biological activity of the compounds both in normal gerbils and in animals exposed to 5 minutes of bilateral carotid occlusion. SeeWO94/00124 and U.S. 5,514,680.

It is known that NMDA receptors are critically involved in the development of persistent pain following nerve and tissue injury. The effects of the NMDA receptor antagonists of the present invention on pain may be evaluated according to WO94/00124 and U.S. 5,514,680.

The compounds of the present invention are useful in treating headaches, in particular, migraine headaches. During migraine attack, a sensory disturbance with unique changes of brain blood flow will result in the development of characteristic migraine auras. Since this unique phenomena has been replicated in animal experiments with cortical-spreading depression (CSD) of Leaó, A.A.P.J., *Neurophysiol.* 7:359-390 (1944), CSD is considered an important phenomena in the pathophysiology of migraine with aura (Tepley *et al.*, In: *Biomagnetism*, eds. S. Williamson, L. Kaufmann, pp. 327-330, Plenum Press, New York (1990)). The CSD is associated with the propagation (2~6 mm/s) of transient changes in electrical activity which relate to the failure of ion homeostasis in the brain, efflux of excitatory amino acids from the neurons and increased energy metabolism (Lauritzen, M., *Acta Neurol. Scand. 76 (Suppl. 113)*:4-40 (1987)). It had been demonstrated the initiation of CSD in a variety of animals including human involved the release of glutamate and could be triggered by NMDA (Curtis *et al.*, *Nature 191*:1010-1011 (1961); and Lauritzen *et al.*, *Brain Res. 475*:317-327 (1988)). Subtype selective NMDA antagonists will be therapeutically useful for migraine headache because of their expected low side effects, their ability to cross blood brain barrier and their systemic bioavailability.

Bladder activity is controlled by parasympathetic pregnaglionic neurons in the sacral spinal cord (DeGroat *et al.*, *J. Auton. Nerv. Sys. 3*:135-160 (1981)). In humans, it has been shown that the highest density of NMDA receptors in the spinal cord are located at sacral level, including those areas that putatively contain bladder parasympathetic pregnaglionic neurons (Shaw *et al.*, *Brain Research 539*:164-168 (1991)). Because NMDA receptors are excitatory in nature, pharmacological blockade of these receptors would suppress bladder activity. It has been shown that the noncompetitive NMDA receptor antagonist MK801 increased the frequency of micturition in rats (Vera and Nadelhaft, *Neuroscience Letters 134*:135-138 (1991)). In addition, competitive NMDA receptor antagonists had also been shown to produce a dose-dependent inhibition of

bladder and of urethral sphincter activity (US Patent 5.192,751). Thus, it is anticipated that subtype selective NMDA receptor antagonists will be effective in the treatment of urinary incontinence mediated by their modulation on the receptor channel activity.

Non-competitive NMDA receptor antagonist MK801 has been shown to be effective in a variety of animal models of anxiety which are highly predictive of human anxiety (Clineschmidt, B.V. *et al., Drug Dev. Res. 2*:147-163 (1982)). In addition, NMDA receptor glycine site antagonists are shown to be effective in the rat protentiated startle test (Anthony, E.W., *Eur. J. Pharmacol. 250*:317-324 (1993)) as well as several other animal anxiolytic models (Winslow, J. *et al., Eur. J. Pharmacol. 190*:11-22 (1990); Dunn, R. *et al., Eur. J. Pharmacol. 214*:207-214 (1992); and Kehne, J.H. *et al., Eur. J. Pharmacol. 193*:283-292 (1981)).

Glycine site antagonists, (+) HA-966 and 5,7-dichlorokynurenic acid were found to selectively antagonize d-amphetamine induced stimulation when injected into rat nucleus accumbens but not in striatum (Hutson, P.H. *et al., Br. J. Pharmacol. 103*:2037-2044 (1991)). Interestingly, (+) HA-966 was also found to block PCP and MK801-induced behavioral arousal (Bristow, L.J. *et al., Br. J. Pharmacol. 108*:156-1163 (1993)). These findings suggest that a potential use of NMDA receptor channel modulators, but not channel blockers, as atypical neuroleptics.

The anxiolytic activity of any particular compound described herein may be determined by use of any of the recognized animal models for anxiety. A preferred model is described by Jones, B.J. *et al., Br. J. Pharmacol. 93*:985-993 (1988).

It has been shown that in an animal model of Parkinson's disease — MPP^+ or methamphetamine-induced damage to dopaminergic neurons — can be inhibited by NMDA receptor antagonists (Rojas *et al., Drug Dev. Res. 29*:222-226 (1993); and Sonsalla *et al. Science 243*:398-400 (1989). In addition, NMDA receptor antagonists have been shown to inhibit haloperidol-induced

catalepsy (Schmidt, W.J. *et al. Amino Acids 1*:225-237 (1991)), increase activity in rodents depleted of monoamines (Carlsson *et al., Trends Neurosci. 13*:272-276 (1990)) and increase ipsilateral rotation after unilateral substantia nigra lesion in rats (Snell, L.D. *et al., J. Pharmacol. Exp. Ther. 235*:50-57 (1985). These are also experimental animal models of Parkinson's disease. In animal studies, the antiparkinsonian agents amantadine and memantine showed antiparkinsonian-like activity in animals at plasma levels leading to NMDA receptor antagonism (Danysz, W. *et al., J. Neural Trans. 7*:155-166, 1994). Thus, it is possible that these antiparkinsonian agents act therapeutically through antagonism of NMDA receptor. Therefore, balance of NMDA receptor activity may be important for the regulation of extrapyramidal function relating to the appearance of parkinsonian symptoms.

Compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is with the skill of the art. Typically, the compounds may be administered to mammals, e.g. humans, orally at a dose of 0.0025 to 50 mg/kg, or an equivalent amount of the pharmaceutically acceptable salt thereof, per day of the body weight of the mammal being treated for psychosis or anxiety disorders, e.g., generalized anxiety disorder, phobic disorders, obsessional compulsive disorder, panic disorder, and post traumatic stress disorders. Preferably, about 0.01 to about 10 mg/kg is orally administered to treat or prevent such disorders. For intramuscular injection, the dose is generally about one-half of the oral dose. For example, for treatment or prevention of anxiety, a suitable intramuscular dose would be about 0.0025 to about 15 mg/kg, and most preferably, from about 0.01 to about 10 mg/kg.

In the method of treatment or prevention of neuronal loss in ischemia, brain and spinal cord trauma, hypoxia, hypoglycemia, and surgery, for the

treatment or prevention of aminoglycoside antibiotic-induced hearing loss, as well as for the treatment of Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease and Down's Syndrome, or in a method of treating a disease in which the pathophysiology of the disorder involves hyperactivity of the excitatory amino acids (e.g. convulsions) or NMDA receptor-ion channel related neurotoxicity, the pharmaceutical compositions of the invention may comprise the compounds of the present invention at a unit dose level of about 0.01 to about 50 mg/kg of body weight, or an equivalent amount of the pharmaceutically acceptable salt thereof, on a regimen of 1-4 times per day. When used to treat chronic pain, to induce anesthesia, or to treat or prevent glaucoma, migraine headache, urinary incontinence, or opiate tolerance or withdrawal, the compounds of the invention may be administered at a unit dosage level of from about 0.01 to about 50mg/kg of body weight, or an equivalent amount of the pharmaceutically acceptable salt thereof, on a regimen of 1-4 times per day. Of course, it is understood that the exact treatment level will depend upon the case history of the animal, e.g., human being, that is treated. The precise treatment level can be determined by one of ordinary skill in the art without undue experimentation.

The unit oral dose may comprise from about 0.01 to about 50 mg, preferably about 0.1 to about 10 mg of the compound. The unit dose may be administered one or more times daily as one or more tablets each containing from about 0.1 to about 10, conveniently about 0.25 to 50 mg of the compound or its solvates.

In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the compounds into preparations which can be used pharmaceutically. Preferably, the preparations, particularly those preparations which can be administered orally and which can

be used for the preferred type of administration, such as tablets, dragees, and capsules, and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from about 0.01 to 99 percent, preferably from about 0.25 to 75 percent of active compound(s), together with the excipient.

Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. Acid addition salts are formed by mixing a solution of the particular NMDA subunit selective antagonist or agonist of the present invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, and the like. Basic salts are formed by mixing a solution of the particular haloperidol analog of the present invention with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

The pharmaceutical compositions of the invention may be administered to any animal which may experience the beneficial effects of the compounds of the invention. Foremost among such animals are mammals, e.g., humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of

conventional mixing, granulating, dragee-making, diss lving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropymethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain

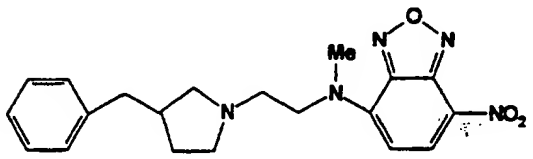
the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules. the active compounds are preferably dissolved or suspended in suitable liquids. such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include. for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The characterization of NMDA subunit binding sites in vitro has been difficult because of the lack of selective drug ligands. Thus, the NMDA ligands of the present invention may be used to characterize the NMDA subunits and their distribution. Particularly preferred NMDA subunit selective antagonists and agonists of the present invention which may be used for this purpose are isotopically radiolabelled derivatives, e.g. where one or more of the atoms are

replaced with ^{3}H, ^{11}C, ^{14}C, ^{15}N, or ^{18}F. Alternatively, a fluorescent group Y may be employed. Examples of such groups include 4-nitrobenzofurazan:



The following examples are illustrative, but not limiting, of the method and compositions of the present invention. The numbering of the compounds in the Examples is independent of the numbering above. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

Examples

Example 1 Preparation of 1-benzyl-3,5(2H,4H)dione-1,4-benzodiazepine

To a solution of 2-benzylanthranilamide (2.9 g, 0.013 mol) in THF (150 ml) were added chloro acetyl chloride (1 ml, 0.013 mol) and K_2CO_3 (7 g, 0.026 mol). The resultant mixture was stirred at 25°C for 10 h then diluted with EtOAc (500 ml) and washed with NH_4Cl (2 x 300 ml), dried and concentrated under reduced pressure. The crude compound was purified by trituration in EtOAc (30 ml) to afford the title compound as a brown solid (3.15 g, 91%). m.p. (dec.) 181°C. ^{1}H NMR (DMSO): 4.805 (s, 2H), 5.646 (m, 2H), 7.155 (d, J = 7.2, 2H), 7.2-7.35 (m, 4H), 7.41-7.51 (m, 2H), 7.68 (t, J = 8.1, 1H), 8.079 (d, J = 7.8, 1H).

Example 2 ***Preparation of 1-benzyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine dihydrochloride***

A solution of 1-benzyl-3,5(2H,4H)dione-1,4-benzodiazepine (3.6 g, 13.5 mmol) in THF (70 ml) was added dropwise to a suspension of $LiAlH_4$ (1.56 g, 39 mmol) in THF (80 ml). The resultant mixture was heated under reflux for 1h then, after cooling at 0°C, the excess reducing agent was decomposed by the dropwise addition of a saturated solution of Na_2SO_4. The mixture was filtered and the filtrate dried and concentrated in vacuo. The crude compound was dissolved in ethanolic hydrogen chloride (10 ml) and acetone was added resulting in the deposition of a crystalline salt that was filtered and washed with acetone to afford the title compound as a white solid (1.0 g, 24%). m.p. 134-136°C (lit.ref. 134-136°C, Iocobelli and Uskokovic, *J. Org. Chem. 27*:3606 (1962)). ^{1}H NMR (D_2O): 3.282 (s, 4H), 4.393 (s, 2H), 4.478 (s, 2H), 7.04 (t, J = 7.2, 1H), 7.171 (d, J = 8.4, 1H), 7.3-7.42 (m, 5H), 7.463 (d, J = 7.2, 2H).

Example 3 ***Preparation of 1-benzyl-4-(3-phenoxypropyl)-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine dihydrobromide***

To a solution of 1-benzyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine dihydrochloride (0.2 g, 0.64 mmol) in DMF (10 ml) were added 3-phenoxypropylbromide (0.15 ml, 0.96 mmol) and potassium carbonate (0.35 g, 2.56 mmol). This heterogeneous solution was heated at 110°C for 5h then cooled at 25°C, diluted with water (50 ml) extracted with ether (2 x 30 ml). The collected organic phase was washed with water (2 x 30 ml), dried and concentrated in vacuum. The crude compound was purified by flash chromatography on silica gel using EtOAc/cyclohexane as eluant to afford the free base as an oil (0.105 g, 44%). ^{1}H NMR ($CDCl_3$): 1.9-2.1 (m, 4H), 2.605 (t,

J = 6.9, 2H), 2.9-3.0 (m, 2H), 3.912 (s, 2H), 4.005 (t, J = 6.3, 2H), 4.349 (s, 2H), 6.85-7.0 (m, 5H), 7.15-7.45 (m, 9H).

The free base (0.1 g. 0.267 mmol) was dissolved in a saturated solution of HBr in MeOH (5 ml) and the resulting solution stirred at 25°C for 15 min. then, after concentration in vacuo, the crude compound was purified by trituration with CH_2Cl_2 to afford the title compound as a solid (0.1 g, 75%). m.p.124-126°C. ^{1}H NMR (DMSO): 2.1-2.3 (m, 2H), 3.1-3.5 (m, 4H), 3.9-4.1 (m, 2H), 4.3-4.6 (m, 2H), 5.235 (bs, 4H), 6.85-7.0 (m, 4H), 7.03 (d, J = 8.1, 1H), 7.2-7.35 (m, 7H), 7.42 (d, J = 7.5, 2H), 9.83 (bs, 1H).

Example 4 Preparation of 1-benzyl-4-(3-hydroxypropyl)-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine

To a solution of 1-benzyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine dihydrochloride (0.25 g, 0.8 mmol) in DMF (10 ml) were added 3-bromo-1-propanol (0.08 ml, 0.88 mmol) and potassium carbonate (0.39 g, 2.8 mmol). This heterogeneous solution was heated at 110°C for 3 h then cooled at 25°C, diluted with water (50 ml) and extracted with ether (2 x 30 ml). The collected organic phase was washed with water (2 x 30 ml), dried and concentrated in vacuum. The crude compound was purified by filtration on silica gel using CH_2Cl_2/MeOH as eluant to afford the title compound as a pale yellow oil (0.18 g, 76%). ^{1}H NMR ($CDCl_3$): 1.55-1.70 (m, 2H), 2.678 (t, J = 5.7, 2H), 2.75-2.85 (m, 2H), 2.9-3.0 (m, 2H), 3.811 (t, J = 4.8, 2H), 3.918 (s, 2H), 4.335 (s, 2H), 6.915 (t, J = 7.2, 1H), 6.98 (d, J = 8.1, 1H), 7.15-7.30 (m, 3H), 7.346 (t, J = 7.2, 2H), 7.41 (d, J = 6.9, 2H).

Example 5 ***Preparation of 1-benzyl-4-(2-phenoxyethyl)-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine dihydrobromide***

To a solution of 1-benzyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine dihydrochloride (0.24 g, 0.77 mmol) in DMF (10 ml) were added 1-*p*-toluensIfonate-2-phenoxyethane (0.17 ml, 0.85 mmol) and potassium carbonate (0.372 g, 2.7 mmol). This heterogeneous solution was heated at 110°C for 24 h then cooled at 25°C, diluted with water (50 ml) extracted with ether (2 x 30 ml). The collected organic phase was washed with water (2 x 30 ml), dried and concentrated in vacuum. The crude compound was purified by flash chromatography on silica gel using EtOAc/cyclohexane as eluant to afford the free base as an oil (0.12 g, 43%). ^{1}H NMR ($CDCl_3$): 2.85-2.9 (m, 4H), 2.9-3.1 (m, 2H), 4.04 (s, 2H), 4.109 (t, J = 0.6, 2H), 4.362 (s, 2H), 6.85-6.95 (m, 4H), 7.0 (d, J = 7.8, 1H), 7.18-7.32 (m, 4H), 7.351 (t, J = 7.2, 2H), 7.43 (d, J = 7.2, 2H).

The HBr salt was prepared as a white solid (0.12 g, 89%); mp 147-149°C. ^{1}H NMR (DMSO): 3.1-3.7 (m, 6H), 4.3-4.65 (m, 6H), 5.219 (bs, 4H), 6.9-7.1 (m, 5H), 7.2-7.35 (m, 7H), 7.35-7.45 (m, 2H), 10.2 (bs, 1H).

Example 6 ***Preparation of N-(4-phenylbutyl)-3,4-dihydroxycinnamide***

To a solution of 542 mg (301 mmol) of 3,4-dihydroxycinnamic acid in 15 mL of anhydrous THF stirred in ice-bath under nitrogen was added portionwise 497 mg (306 mmol) of 1,1-carbonyldiimidazole (CDI) and the solution was stirred for 0.5 h. To the solution was added dropwise 491 mg (3.29 mmol) of 4-phenylbutylamine and it was stirred in ice-bath for 2 h and at rt overnight. The solution was diluted by water (50 mL) and ethyl acetate (40 mL). The organic phase was saparated and washed by 0.1 N HCl (3 x 15 mL), dried ($MgSO_4$) and evaporated to leave white solid. The solid was crystallized from ethanol (10 mL) to give 178 mg (19%) of the title compound as a white solid, mp 165-6°C. ^{1}H

NMR (DMSO-d_6), 1.48 (m, 2H), 1.61 (m, 2H), 2.581 (t, J = 7.5, 2H), 3.053 (q, J = 6.3, 2H), 6.308 (d, J = 15.9, 1H), 6.964 (m, 1H), 6.978-7.296 (m, 7H), 7.468 (d, J = 15.9, 1H), 7.660 (t, J = 5.4, 1H), 9.766 (s, 1H), 12.336 (mb, 1H).

Example 7 Preparation of N-(4-phenylbutyl)cinnamide

From 445 mg (3.00 mmol) of cinnamic acid, 486 mg (3.00 mmol) of CDI and 551 mg (3.69 mmol) of 4-phenylbutylamine there was obtained 303 mg (36%) of the title compound as a white solid, mp 62-63°C. ^{1}H NMR ($CDCl_3$), 1.56-1.70 (m, 4H), 2.660 (t, J = 7.2, 2H), 3.410 (q, J = 6.3, 2H), 5.610 (sb, 1H), 6.360 (d, J = 15.6, 1H), 7.169-7.510 (m, 10H), 7.618 (d, J = 15.3, 1H).

Example 8 Preparation of N-(4-phenylbutyl)-4-hydroxycinnamide

From 492 mg (3.00 mmol) of 4-hydroxycinnamic acid, 496 mg (3.05 mmol) of CDI and 490 mg (3.25 mmol) of 4-phenylbutylamine there was obtained 82 mg (9%) of the title compound as a white solid, mp 140-1°C. ^{1}H NMR ($CDCl_3$+DMSO-d_6), 1.484-1.585 (m, 4H), 2.540 (t, J = 7.2, 2H), 3.253 (q, J = 6.2, 2H), 6.175 (d, J = 15.9, 1H), 6.35 (sb, 1H), 6.724 (d, J = 8.4, 2H), 7.071 (d, J = 7.2, 1H), 7.150 (d, J = 6.6, 2H), 7.230-7.267 (m, 3), 7.396 (d, J = 15.6, 1H), 9.018 (s, 1H).

Example 9 Preparation of 4'-benzylpiperidinyl-4-hydroxycinnamide

From 494 mg (3.01 mmol) of 4-hydroxycinnamic acid, 488 mg (3.01 mmol) of CDI and 614 mg (3.50 mmol) of 4-benzylpiperidine there was obtained 184 mg (19%) of the title compound as a white solid, mp 138-40°C. ^{1}H NMR ($CDCl_3$), 1.218 (m, 2H), 1.772 (m, 3H), 2.567 (m, 3H), 3.048 (m, 1H), 4.112 (m, 1H), 4.689 (m, 1H), 6.125 (m, 1), 6.746 (d, J = 15.6, 1H), 6.845 (d, J = 8.4, 2H),

7.146 (d, J = 6.6, 2H), 7.301 (m, 3H), 7.398 (d, J = 8.7, 2H), 7.597 (d, J = 15.3, 1H).

Example 10 Preparation of N-(4-phenylbutyl)-3-(4-hydroxyphenyl)-propionamide

From 499 mg (3.01 mmol) of 3-(4-hydroxyphenyl)propionic acid, 488 mg (3.01 mmol) of CDI and 498 mg (3.34 mmol) of 4-phenylbutylamine there was obtained 86 mg (10%) of the title compound as a white solid, mp 71-2°C. ^{1}H NMR ($CDCl_3$), 1.472 (m, 2H), 1.567 (m, 2H), 2.412 (t, J = 7.5, 2H), 2.598 (t, J = 7.2, 2H), 2.880 (t, J = 7.2, 2H), 3.228 (q, J = 6.6, 2H), 5.287 (s, 1H), 5.381 (s, 1H), 6.723 (d, J = 8.1, 2H), 7.040 (d, J = 8.4, 2H), 7.171 (m, 3H), 7.292 (m, 2H).

Example 11 Preparation of 1,3-Bis(4-hydroxybenzylidene)acetone

A solution of 488 mg (4.00 mmol) of 4-hydroxybenzaldehyde and 116 mg (2.00 mmol) of acetone with 2 drop of piperidine in 10 mL of ethanol was refluxed for 2 days. The resulting red solution was added into 40 mL of water and stirred for 2 h. The mixture was filtered and the solid was washed by water, dried to leave red solid 510 mg. The solid was crystallized twice from ethanol/water to give 332 mg (62%) of the title compound as a brown solid, mp 210-1°C. ^{1}H NMR (DMSO-d_6), 6.829 (d, J = 8.4, 4H), 7.095 (d, J = 16.2, 2H), 7.618 (d, J = 8.1, 4H), 7.657 (d, J = 15.3, 2H), 10.042 (mb, 2).

Example 12 Preparation of 4-Chloro-N-(2-(4-hydroxyphenyl)ethyl)-cinnamide

A solution of 4-chlorocinnamoyl chloride (267 mg, 1.33 mmol) and tyramine (532 mg, 3.88 mmol) in CH_3CN (20 mL) was refluxed for 3 h. The

solvent was removed from the resulting solution in vacuo and the residue was partitioned between water (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined CH_2Cl_2 solution was washed with water (50 mL), dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the resulting brown powder (CH_2Cl_2/MeOH, 8:1, 30 g silica) yielded the title compound (195 mg, 49%). A portion was crystallized from EtOAc: mp 164-167°C; ^{1}H NMR (DMSO-d_6) δ 2.06 (t, J = 7.2, 2 H), 3.18 (m, 2 H), 6.55 (d, J = 7.2, 1 H), 6.63 (d, J = 8.1, 2 H), 6.96 (d, J = 8.1, 2 H), 7.33 (d, J = 15.9, 1 H), 7.42 (d, J = 8.1, 2 H), 7.23 (d, J = 8.4, 2 H), 8.12 (bs, 1 H).

Example 13 Preparation of 4-Chloro-N-(1-(indol-3-yl)prop-2-yl)cinnamide

From 4-chlorocinnamoyl chloride (105 mg, 0.522 mmol) and (±)-α-methyltryptamine (100 mg, 0.573 mmol) there was obtained the title compound (72 mg, 37%) as colorless powder. A portion was crystallized from EtOAc: mp 170-172°C; ^{1}H NMR (DMSO-d_6) δ 1.23 (d, J = 6.6, 3 H), 3.01 (d, J = 5.1, 2 H), 4.52 (h, J = 3.6, 1 H), 5.52 (bd, J = 7.5, 1 H), 6.22 (d, J = 15.6, 1 H), 7.00-7.50 (m, 10 H), 7.52 (d, J = 15.6, 1 H), 7.67 (d, J = 7.8, 1 H), 8.08 (bs, 1 H).

Example 14 Preparation of 4-Chloro-N-(3-phenylpropyl)cinnamide

From 4-chlorocinnamoyl chloride (179 mg, 0.890 mmol) and 3-phenylpropylamine (524 mg, 3.88 mmol) there was obtained the title compound (250 mg, 93%) as colorless powder. A portion was crystallized from EtOAc: mp 121-122°C; ^{1}H NMR (DMSO-d_6) δ 1.92 (p, J = 7.2, 2 H), 2.70 (t, J = 7.8, 2 H), 3.42 (q, J = 6.9, 2 H), 5.59 (bs, 1 H), 6.26 (d, J = 15.6, 1 H) 7.00-7.40 (m, 10 H), 7.53 (d, J = 15.6, 1 H).

Example 15 Preparation of 4-Chloro-N-(3-hydroxypropyl)cinnamide

A solution of 4-chlorocinnamic acid (730 mg, 4.09 mmol) in $SOCl_2$ (5 mL) was refluxed overnight. The $SOCl_2$ was mostly removed in vacuo (vacuum pump) to give a colorless powder. The powder was dissolved in CH_2Cl_2 (10 mL) and the solvent was removed in vacuo (vacuum pump) while the solution was being magnetically stirred. Upon the complete evaporation of the CH_2Cl_2, the resulting powder was dissolved in CH_2Cl_2 (20 mL). Neat 3-amino-1-propanol (408 mg, 8.16 mmol) was slowly added and the mixture was refluxed for 3 h. The solvent was removed *in vacuo* to give a colorless powder. This was crystallized twice from EtOAc to yield the title compound as a colorless powder (791 mg, 67%): mp 140-141°C; ^{1}H NMR (DMSO-d_6) δ 1.59 (p, J = 6.6, 2 H), 3.18 (q, J = 6.6, 2 H), 3.42 (q, J = 6.0, 2 H), 4.46 (1 H), 6.64 (d, J = 15.6, 1 H), 7.44 (d, J = 15.6, 1 H), 7.56 (d, J = 8.1, 2 H), 7.58 (d, J = 8.4, 2 H), 8.10 (s, 1 H).

Example 16 Preparation of 2,5-Dichloro-N-(4-phenylbutyl)cinnamide

A) **2,5-Dichlorocinnamic acid.** A mixture of 1,4-dichloro-2-iodobenzene (2.8 g, 10 mmol), acrylic acid (890 mg, 12 mmol), palladium(II)acetate (22 mg, 0.10 mmol) and Et_3N (2.6 g, 26 mmol) in CH_3CN (4 mL) was heated under N_2 in a sealed tube at 100°C for 1 h. The reaction was allowed to cool to rt and was diluted with HCl (10% in water, 250 mL). The resulting colorless precipitate was collected by filtration and was crystallized from EtOH to yield the title compound as a solid (1.7 g, 75%): ^{1}H NMR ($CDCl_3$) δ 6.67 (d, J = 16.2, 2 H), 7.45 (d, J = 8.7, 2 H), 7.53 (d, J = 8.4, 2 H), 7.71 (d, J = 15.9, 2 H), 8.01 (s, 1 H).

B) From 2,5-dichlorocinnamic acid (364 mg, 1.68 mmol), $SOCl_2$ (5 mL) and 4-phenylbutylamine (499 mg, 3.35 mmol) there was obtained the title compound as a solid (249 mg, 45%): mp 92-93°C; ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 4 H), 2.66

(t, J = 6.9, 2 H), 4.40 (m, 2 H), 5.60 (bs, 1 H), 6.32 (d, J = 15.6, 1 H), 7.00-7.40 (m, 7 H), 7.53 (s, 1 H), 7.87 (d, J = 15.6, 1 H).

Example 17 Preparation of α-Cyano-N-(4-phenylbutyl)cinnamide

A) 2-Cyano-N-(4-phenylbutyl)acetamide. A solution of ethyl 2-cyanoacetate (8.0 g, 7.5 mL, 70 mmol) and 4-phenylbutylamine (10 g, 67 mmol) was allowed to stir at 100°C for 10 hr in an open vessel. The residue was purified by flash chromatography to give the title compound as a yellow solid (10 g, 69%): mp 50-52°C; ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 4 H), 2.65 (m, 2 H), 3.31 (m, 2 H), 3.35 (s, 2 H), 6.07 (bs, 1 H), 7.16-7.29 (m, 5 H).

B) To a solution of benzaldehyde (530 mg, 5.00 mmol) and 2-cyano-N-(4-phenylbutyl)acetamide (1.19 g, 5.50 mmol) in 20 mL of absolute EtOH was added piperidine (5 drops). The resulting solution was allowed to reflux for 3 h. The EtOH was evaporated in vacuo to give a residue. The residue was purified by flash chromatography to give the title compound as a colorless solid (450 mg, 30%): mp 75-77°C; ^{1}H NMR ($CDCl_3$) δ 1.68 (m, 4 H), 2.67 (m, 2 H), 3.46 (m, 2 H), 6.35 (bs, 1 H), 7.20-7.29 (m, 5 H), 7.52 (m, 3 H), 7.92 (d, J = 6.9, 2 H), 8.33 (s, 1 H).

Example 18 Preparation of α-Cyano-4-hydroxy-N-(4-phenylbutyl)-cinnamide

From 4-hydroxybenzaldehyde (610 mg, 5.00 mmol) and 2-cyano-N-(4-phenylbutyl)acetamide (1.19 g, 5.50 mmol) there was obtained the title compound as a yellow solid (810 mg, 51%): mp 143-145°C; ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 4 H), 2.66 (m, 2 H), 3.43 (m, 2 H), 6.12 (bs, 1 H), 6.33 (s, 1 H), 6.93 (d, J = 8.7, 2 H), 7.19-7.29 (m, 5 H), 7.87 (d, J = 8.7, 2 H), 8.23 (s, 1 H).

Example 19 Preparation of α-Cyano-3-hydroxy-N-(4-phenylbutyl)-cinnamide

From 3-hydroxybenzaldehyde (610 mg, 5.00 mmol) and 2-cyano-N-(4-phenylbutyl)acetamide (1.19 g, 5.50 mmol) there was obtained the title compound as a colorless solid (1.18 g, 74%): mp 183-185°C; ^{1}H NMR ($CDCl_3$) δ 1.48 (m, 4 H), 2.49 (m, 2 H), 3.23 (m, 2 H), 6.83-7.26 (m, 11 H), 8.00 (m, 1 H).

Example 20 Preparation of α-Cyano-4-fluoro-N-(4-phenylbutyl)cinnamide

From 4-fluorobenzaldehyde (620 mg, 5.00 mmol) and 2-cyano-N-(4-phenylbutyl)acetamide (1.19 g, 5.50 mmol) there was obtained the title compound as a yellow solid (800 mg, 50%): mp 82-84°C; ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 4 H), 2.67 (m, 2 H), 3.46 (m, 2 H), 6.32 (bs, 1 H), 7.79 (m, 7 H), 7.95 (m, 2 H), 8.28 (s, 1 H).

Example 21 Preparation of 4-Chloro-α-cyano-N-(4-phenylbutyl)cinnamide

From 4-chlorobenzaldehyde (702 mg, 5.00 mmol) and 2-cyano-N-(4-phenylbutyl)acetamide (1.19 g, 5.50 mmol) there was obtained the title compound as a colorless solid (830 mg, 49%): mp 115-117°C; ^{1}H NMR ($CDCl_3$) δ 1.64 (m, 4 H), 2.67 (m, 2 H), 3.46 (m, 2 H), 6.33 (bs, 1 H), 7.20-7.32 (m, 5 H), 7.48 (d, J = 8.4, 2 H), 7.88 (d, J = 8.4, 2 H), 8.27 (s, 1 H).

Example 22 Preparation of N-(2-Phenylethyl)-N-(3-phenylpropyl)amine

A mixture of phenylethylamine (770 mg, 6.0 mmol), 3-phenylpropyl bromide (599 mg, 3.0 mmol) and NaI (253 mg) in toluene (15 mL) was refluxed for 18 h, then cooled to rt. The mixture was diluted with EtOAc (30 mL), then filtered. The filtrate was evaporated and the residue was chromatographed over silica gel (EtOAc-EtOH, 85: 15) to give 160 mg (9.6%) of the amine as a yellowish oil. ^{1}H NMR ($CDCl_3$): 1.32-1.40 (m, 2H), 1.46 (bs, 1H, NH), 1.67-1.86 (m, 2H), 2.60-2.69 (m, 4H), 2.78-2.91 (m, 2H), 7.14-7.33 (m, 10H). Hydrochloride, mp 270-2°C.

Example 23 Preparation of N-(1-Methyl-2-hydroxy-2-phenylethyl)-N-(3-phenylpropyl)amine

From (1S,2R)-(+)-norephedrine (990 mg, 6.5 mmol) and 3-phenylpropyl bromide (647 mg, 3.25 mmol) there was obtained 80 mg (9%) of the amine as a yellow oil. ^{1}H NMR ($CDCl_3$): 0.821 (d, 3H, J=6.5), 1.81-1.89 (m, 4H), 2.62-2.84 (m. 4H). 2.90-2.96 (m, 1H), 4.764 (d,1H, J=4), 7.19-7.34 (m, 10H).

Example 24 N-(3-Phenoxypropyl)-N-(1-phenylcyclohexyl)amine

A mixture of K_2CO_3 (170 mg, 1.23 mmol), 3-phenoxypropyl bromide (241 mg, 1.01 mmol) and 1-amino-1-phenylcyclohexane (352 mg, 2.01 mmol) in toluene (15 mL) was refluxed for 24 h, then cooled to rt. The mixture was filtered, and the filtrate was evaporated. The residue was chromatographed over silica gel (EtOAc-EtOH, 10 : 0.5) to give 165 mg (26.7%) of the amine as a yellowish oil. ^{1}H NMR ($CDCl_3$): 1.26-1.35 (m, 2H), 1.48-1.68 (m, 6H), 1.79-1.86 (m, 5H), 2.360 (t, 2H, J=6.5), 3.974 (t, 2H, J=6.5). The hydrochloride, mp

186-187°C. Analysis, Calcd. for ($C_{21}H_{27}NO$ +HCl): C, 72.92, H 8.16, N 4.05; Found: C 73.04, H 8.22, N 3.93.

Example 25 ***Bis-N,N-(2-(4-fluorophenoxy)ethyl)-N-(2-(4-hydroxyphenyl)-ethyl)amine hydrochloride***

From tyramine (831 mg, 6.07 mmol) and 2-(4-fluorophenoxy)ethyl bromide (1.33 g, 6.06 mmol) there was obtained the title compound as an oil (384 mg, 23%). The hydrochloride, mp 130-132°C; ^{1}H NMR ($CDCl_3$) 2.77 (t, J = 6.6, 2 H), 2.93 (t, J = 6.6, 2 H), 3.01 (t, J = 4.8, 2 H), 4.02 (t, J = 4.8, 2 H), 6.50-7.20 (m, 8 H).

Example 26 ***N-(3-(4-Chlorophenyl)propyl)-N-(2-(2-fluorophenoxy)ethyl)-N-(3-hydroxypropyl)amine hydrochloride***

A) ***N-(3-(4-Chlorophenyl)propyl)-N-(3-hydroxypropyl)amine.*** $LiAlH_4$ (64.5 mg, 1.70 mmol) was added to freshly distilled THF (10 mL). A solution of 4-chloro-*N*-(3-hydroxypropyl)cinnamamide (145 mg, 0.567 mmol) in freshly distilled THF (10 mL) was slowly added to the $LiAlH_4$ suspension with stirring at rt. After addition, the mixture was refluxed for 8 h. H_2O (10 mL) was added to the mixture followed by NaOH (15% in H_2O, 4 mL). The resulting precipitate was removed by filtration. The solvent was removed from the filtrate *in vacuo*. The resulting yellow oil was partitioned between H_2O (25 mL) and ether (25 mL). The aqueous phase was separated and was extracted twice with ether (25 mL). The combined ether extract was washed with H_2O (50 mL), dried over Na_2SO_4 and was concentrated *in vacuo*. Flash chromatography of the resulting yellow oil (EtOAc) yielded of the title compound as a yellow oil (103 mg, 74%): ^{1}H NMR ($CDCl_3$) 1.72 (p, *J* = 5.4, 2 H), 1.81 (p, *J* = 7.5, 2 H), 2.63 (q, *J* = 7.5, 4 H), 2.89 (t, *J* = 5.7, 2 H), 3.81 (t, *J* = 5.4, 2 H), 7.11 (d, *J* = 8.1, 2 H), 7.26 (d, *J* = 8.1, 2 H).

B) From *N*-(3-(4-chlorophenyl)propyl)-N-(3-hydroxypropyl) amine (665 mg, 2.92 mmol) and 2-(2-fluorophenoxy)ethyl bromide (796 mg, 3.65 mmol) there was obtained the title compound as an oil (585 mg, 55%). The hydrochloride, mp 101-103°C; ^{1}H NMR ($CDCl_3$) 1.71 (p, J = 5.4, 2 H), 1.82 (p, J = 5.4, 2 H), 2.59 (m, 4 H), 2.76 (t, J = 2.7, 2 H), 2.92 (t, J = 5.7, 2 H), 3.80 (t, J = 5.1, 2 H), 4.09 (t, J = 5.4, 2 H), 4.60 (s, 1 H), 6.80-7.40 (m, 8 H).

Example 27 ***N-(3-(4-Chlorophenyl)propyl)-N-(2-(4-fluorophenoxy)ethyl)-N-(3-hydroxypropyl)amine hydrochloride***

From *N*-(3-(4-chlorophenyl)propyl)-*N*-(3-hydroxypropyl)amine (665 mg, 2.92 mmol) and 2-(4-fluorophenoxy)ethyl bromide (796 mg, 3.65 mmol) there was obtained the title compound as an oil (586 mg, 55%). The hydrochloride, mp 81-83°C; ^{1}H NMR ($CDCl_3$) 1.71 (p, J = 4.5, 2 H), 1.84 (p, J = 6.6, 2 H), 2.57 (m, 4 H), 2.73 (t, J = 2.1, 2 H), 2.85 (t, 2 H), 3.82 (t, J = 4.5, 2 H), 3.97 (t, J = 5.4, 2 H), 4.80 (s, 1 H), 6.80-7.40 (m, 8 H); HRMS calcd for $C_{20}H_{25}ClFNO_2$ 365.1562, found 365.1560.

Example 28 ***1-Benzyl-3-(2-fluorobenzylidene)pyrrolidine hydrochloride***

A) 2-Fluorobenzyltriphenylphosphonium bromide. To a solution of triphenylphosphine (26.2 g, 0.1 mol) in 100 mL of ether was added 2-fluorobenzyl bromide (18.9 g, 0.1 mol). The resulting solution was allowed to stir at rt overnight. The white solid was collected by filtration and dried to give 38 g (84%) of the product as a white solid. mp 220-222°C. ^{1}H NMR ($CHCl_3$) 5.476 (d, J = 14.4, 2 H), 6.80 (dd, J_1 = 9.0, J_2 = 9.3, 1 H), 6.984 (dd, J_1 = 7.8, J_2 = 7.5, 1 H), 7.220 (m, 1 H), 7.524 (m, 1 H), 77.626 (m, 6 H), 7.759 (m, 9 H).

B) 1-Benzyl-3-(2-fluorobenzylidene)pyrrolidine hydrochloride. To a 250-mL three-necked round bottom flask was added 0.64 g (60% in mineral oil) of sodium

hydride and 15 mL of dry DMSO under N_2. The mixture is heated at 80°C for 1 hr. The resulting solution was cooled in an ice-water bath. To this solution was added a suspension of 2-fluorobenzyltriphenylphosphonium bromide (8.2 g, 0.018 mol) in 80 mL of warm DMSO. The resulted solution was stirred at 0 °C for 10 min and at rt for 15 min. Then 3-benzylpyrrolidinone (2.63 g, 15 mol) was added dropwise under N_2. The resulting mixture was allowed to stir at 80°C overnight. Then the mixture was poured into ice (200 g) and extracted with ether (3 x 100 mL). The combined extracts was dried over sodium sulfate. The solvent was evaporated in vacuo to give a residue, which was purified by flash chromatography (eluent 5 % EtOAc in hexanes), giving 2.5 g (63%) of the product as a pale yellow oil, 200 mg of which was dissolved into 10 mL of methanol and 2 mL of 1 M HCl in methanol was added. Evaporation of methanol gave a residue, to which was added 30 mL of ether. A white solid was collected by filtration and dried to give 230 mg (100%) of the title product. mp 187-189°C. ^{1}H NMR ($CHCl_3$) 2.903-3.167 (m, 3 H), 3.681 (m, 2 H), 4.152-4.428 (m, 3 H), 6.653 (s, 1 H), 7.144 (m, 3 H), 7.283 (m,1 H), 7.145 (m, 3 H), 7.618 (m, 2H), 13.3 (brs, 1 H).

Example 29 1-[2-(4-Benzyloxyphenoxy)ethyl]-3- (2-fluorobenzyl)pyrrolidine hydrochloride

A) 1-Benzyl-3-(2-fluorobenzyl)pyrrolidine hydrochloride. To a solution of 1-benzyl-3-(2-fluorobenzylidene)pyrrolidine (1.34 g, 5.0 mmol) in 50 mL of methanol was added 100 mg of PtO_2. The resulting mixture was hydrogenated at 40 psi for 8 h. The catalyst was removed through a short column of Celite (10 g) and was washed with methanol (3 x 20 mL). The filtrate was evaporated in vacuo and dissolved into 20 mL of methanol, to which was added 24 mL of 1 M HCl in methanol. The resulting solution was stirred for 10 min. Evaporation of methanol gave a residue, to which was added 60 mL of ether and stirred

overnight. Evaporation of solvent gave a colorless oil. ^{1}H NMR ($CHCl_3$) 1.625 (m, 3 H), 2.734 (m, 2 H), 2.933 (m, 2 H), 3.489 (m, 2 H), 3.650 (m, 2 H), 7.134 (m, 3 H), 7.264 (m, 2 H), 7.357 (m, 2 H), 7.619 (m, 2 H), 12.8 (brs, 1 H).

B) 3-(2-Fluorobenzyl)pyrrolidine hydrochloride. A mixture of 1-benzyl-3-(2-fluorobenzyl)pyrrolidine hydrochloride (1.53 g, 5.0 mmol) and 0.66 g of 10% Pd/C in 50 mL of 95% ethanol was hydrogenated at 50 psi for 12 h. The catalyst was removed through a short column of Celite (10 g) and was washed with methanol (3 x 20 mL). The filtrate was evaporated in vacuo to give a residue. To which was added ether (50 mL). The resulting mixture was allowed to stir overnight. Evaporation of solvent gave a clear oil. ^{1}H NMR ($CHCl_3$) 1.769 (m, 2 H), 2.113 (m, 1 H), 2.659-2.959 (m, 4 H), 3.391 (m, 2 H), 6.995-7.204 (m, 4 H), 9.80 (s, 2 H).c)

C) 1-[2-(4-Benzyloxyphenoxy)ethyl]-3-(2-fluorobenzyl)pyrrolidine hydrochloride. A mixture of 2-(4-benzyloxyphenoxy)ethyl bromide (0.46 g, 1.50 mmol), 3-(2-fluorobenzyl)pyrrolidine hydrochloride (0.323 g, 1.50 mmol), potassium carbonate (0.518 g, 3.8 mmol) in 30 mL of acetonitrile was allowed to reflux for 12 h. The inorganic salt was removed through a short column of silica gel and washed with ethyl acetate (3 x 25 mL). The combined filtrate was evaporated in vacuo to give a crude mixture, which was purified by flash chromatography (20% methanol in ethyl acetate) to give an oil, to which was added 3 mL of 1M HCl in methanol. Evaporation of methanol gave a residue, to which was added ether (30 mL) and was allowed to stir overnight. An off white solid was collected by filtration and dried in vacuo to give 0.25 g (38%) of the title product; mp 116-118 °C. ^{1}H NMR ($CDCl_3$) 1.823-2.303 (m, 3 H), 2.819 (m, 1 H), 2.944 (m, 3 H), 3.421 (m, 2 H), 3.857 (m, 2 H), 4.438 (m, 2 H), 5.015 (s, 2 H), 6.818-6.881 (m, 4 H), 7.063 (m, 2 H), 7.261 (m, 2 H), 7.407 (m, 5 H), 12.869 (brs, 1 H). Anal. Calcd for $C_{26}H_{29}ClFNO_2.0.5H_2O$: C, 69.24; H, 6.70; N, 3.11. Found: C, 69.15; H, 6.45; N, 3.11.

Example 30 1-[2-(4-hydroxyphenoxy)ethyl]-3-(2-fluorobenzyl)pyrrolidine hydrochloride

To a solution of 1-[2-(4-benzyloxyphenoxy)ethyl]- 3-(2-fluorobenzyl)-pyrrolidine (0.2 g, 0.45 mmol) in 30 mL of methanol was added 0.050 g of 20% $Pd(OH)_2$. The resulting mixture was hydrogenated at 30 psi of hydrogen for 4 h. The catalyst was removed through a short column of Celite (5 g) and washed with methanol (3 x 15 mL). Evaporation of methanol gave a residue, to which was added ether (100 mL). The resulting mixture was allowed to stir at rt overnight. The off white solid was collected by filtration and dried in vacuo, giving 0.125 g (79%) of the title product, mp 75-77°C. ^{1}H NMR (CD_3OD) 1.70 (m, 2 H), 2.0 (m, 2 H), 2.675 (m, 3 H), 3.417 (m, 4 H), 4.025 (m, 2 H), 6.521 (d, J = 9.0, 2 H), 6.635 (d, J = 9.0, 2 H), 6.943 (m, 2 H), 7.089 (m, 2 H). Anal. Calcd for $C_{19}H_{23}ClFNO_2.0.7H_2O$: C, 62.61; H, 6.75; N, 3.84. Found: C, 62.60; H, 6.51; N, 4.19.

Example 31 1-[2-(4-Benzyloxy-3-fluorophenoxy)ethyl]-3-(2-fluorobenzyl)-pyrrolidine hydrochloride

From a mixture of 2-(4-benzyloxy-3-fluorophenoxy)ethyl bromide (0.49 g, 1.50 mmol), 3-(2-fluorobenzyl)pyrrolidine hydrochloride (0.323 g, 1.50 mmol), potassium carbonate (0.518 g, 3.8 mmol) in 30 mL of acetonitrile was obtained 0.25 g (38%) of the title compound as an off white solid, mp 120-122°C. ^{1}H NMR ($CDCl_3$) 1.80-2.18 (m, 2 H), 2.792-2.923 (m, 5 H), 3.407 (m, 2 H), 3.803 (m, 2 H), 4.410 (s, 2 H), 5.055 (s, 2 H), 6.540-6.663 (m, 4 H), 6.882-7.037 (m, 3 H), 7.327 (m, 5 H), 12.8 (brs, 1 H). Anal. Calcd for $C_{26}H_{29}ClFNO_2$: C, 67.89; H, 6.14; N, 3.07. Found: C, 67.69; H, 6.22; N, 2.99.

Example 32 1-[2-(3-Fluoro-4-hydroxyphenoxy)ethyl]-3-(2-fluorobenzyl)-pyrrolidine maleic acid salt

A mixture of 1-[2-(4-benzyloxy-3-fluorophenoxy)ethyl]-3-(2-fluorobenzyl)pyrrolidine hydrochloride (0.2 g, 0.44 mmol) in 30 mL of methanol with 0.050 g of 20% $Pd(OH)_2$ was hydrogenated at 30 psi of hydrogen for 4 h and worked up to gave the free base as brown oil. The oil was redissolved into 5 mL of methanol and 60.5 mg (0.52 mmol) of maleic acid was added and was allowed to stir at rt for 10 min. Evaporation of methanol gave a residue, to which was added ether (50 mL). The resulting mixture was allowed to stir at rt overnight. The off white solid was collected by filtration, and dried in vacuo, giving 0.163 g (84%) of the title compound, mp 63-65°C. ^{1}H NMR (CD_3OD) 1.70 (m, 2 H), 2.0 (m, 2 H), 2.656 (m, 4 H), 3.0 (m, 2 H), 3.402 (m, 4 H), 4.012 (d, J = 5.1 Hz, 2 H), 6.044 (m, 2 H), 6.462 (m, 2 H), 6.557-6.664 (m, 2 H), 6.925 (m, 2 H), 7.074 (m, 2 H). Anal. Calcd for $C_{23}H_{25}F_2NO_6.0.8H_2O$: C, 59.54; H, 5.78; N, 3.02. Found: C, 59.42; H, 5.51; N, 2.89.

Example 33 1-[2-(4-Benzyloxy-3-methylphenoxy)ethyl]-3-(2-fluorobenzyl)-pyrrolidine hydrochloride

From a mixture of 2-(4-benzyloxy-3-methylphenoxy)ethyl bromide (0.36 g, 1.13 mmol), 3-(2-fluorobenzyl)pyrrolidine hydrochloride (0.24 g, 1.12 mmol), potassium carbonate (0.386 g, 2.8 mmol) in 30 mL of acetonitrile was obtained 0.24 g (47%) of the title compound as an off white solid, mp 146-148°C. ^{1}H NMR ($CDCl_3$) 1.80 (m, 2 H), 2.233 (m, 3 H), 2.797-2.954 (m, 5 H), 3.411 (m, 2 H), 3.90 (m, 2 H), 4.415 (s, 2 H), 5.002 (s, 2 H), 6.756 (m, 4 H), 7.048 (m, 3 H), 7.295 (m, 5 H), 12.9 (brs, 1 H). Anal. Calcd for $C_{27}H_{31}ClFNO_3.0.2H_2O$: C, 70.55; H, 6.89; N, 3.05. Found: C, 70.64; H, 7.08; N, 3.23.

Example 34 1-[2-(4-Hydroxy-3-methylphenoxy)ethyl]-3-(2-fluorobenzyl)-pyrrolidine maleic acid salt

A mixture of 1-[2-(4-benzyloxy-3-methylphenoxy)ethyl]-3-(2-fluorobenzyl)pyrrolidine hydrochloride (0.2 g, 0.44 mmol) in 30 mL of methanol with 0.050 g of 20% $Pd(OH)_2$ was hydrogenated at 30 psi of hydrogen for 4 h and worked up to give 0.140 g (95%) of the title compound as off white solid, mp 98-100°C. ^{1}H NMR (CD_3OD) 1.70 (m, 1 H), 1.945 (m, 3 H), 2.643 (m, 3 H), 3.120 (m, 3 H), 3.382 (m, 4 H), 3.977 (d, J = 3.9, 2 H), 6.028 (m, 2 H), 6.446 (m, 2 H), 6.522 (m, 1 H), 6.915 (m, 2 H), 7.074 (m, 2 H). Anal. Calcd for $C_{24}H_{28}FNO_6.0.3H_2O$: C, 63.93; H, 6.39; N, 3.11. Found: C, 63.90; H, 6.28; N, 3.05.

Example 35 1-[2-(4-Benzyloxyphenoxy)ethyl]-3-(4-methylbenzyl)pyrrolidine hydrochloride

A) 3-(4-Methylbenzyl)pyrrolidine was prepared from 4-methylbenzyltriphenylphosphonium bromide (8.1 g, 0.018 mol) and 3-benzylpyrrolidinone (2.63 g, 15 mol) in three steps as a clear oil. ^{1}H NMR ($CHCl_3$) 1.43 (m, 2 H), 1.86 (m, 2 H), 2.32 (s, 3 H), 2.58 (m, 3 H), 2.97 (m, 2 H), 7.07 (s, 4 H).

B) 1-[2-(4-Benzyloxyphenoxy)ethyl]-3-(4-methylbenzyl)pyrrolidine hydrochloride was prepared from a mixture of 2-(4-benzyloxyphenoxy)ethyl bromide (0.61 g, 2.0 mmol), 3-(4-methylbenzyl)pyrrolidine (0.35 g, 2.0 mmol), potassium carbonate (0.69 g, 5.0 mmol) in 30 mL of acetonitrile as a white solid (0.23 g, 26%), mp 148-151°C. ^{1}H NMR ($CDCl_3$) 1.80 (m, 1 H), 2.01 (m, 2 H), 2.32 (s, 3 H), 2.71 (m, 2 H), 2.88 (m, 3 H), 3.41 (m, 3 H), 3.85 (m, 2 H), 4.44 (m, 2 H), 6.81 (m, 2 H), 6.91 (m, 2 H), 7.10 (m, 4 H), 7.38 (m, 5 H), 12.80 (brs, 1 H).

Example 36 ***1-[2-(4-Hydroxyphenoxy)ethyl]- 3-(4-methylbenzyl)pyrrolidine maleic acid salt***

A mixture of 1-[2-(4-benzyloxyphenoxy)ethyl]-3-(4-methylbenzyl)pyrrolidine hydrochloride (0.15 g, 0.34 mmol) in 30 mL of methanol with 0.038 g of 20% $Pd(OH)_2$ was hydrogenated at 30 psi of hydrogen for 4 h and worked up to give 0.14 g (97%) of the title product as white solid, mp 102-105°C. ^{1}H NMR (CD_3OD) 1.78 (m, 2 H), 2.10 (m, 2 H), 2.22 (s, 3 H), 2.68 (s, 3 H), 3.51 (m, 4 H), 4.12 (m, 2 H), 6.17 (s, 2 H), 6.65 (m, 2 H), 6.73 (m, 2 H), 7.03 (m, 4 H).

Example 37 ***1-[2-(4-Benzyloxyphenoxy)ethyl]-3-(4-fluorobenzyl)pyrrolidine hydrochloride***

A) **3-(4-Fluorobenzyl)pyrrolidine** was prepared from 4-fluorobenzyltriphenylphosphonium bromide (8.2 g, 0.018 mol) and 3-benzylpyrrolidinone (2.63 g, 15 mol) in three steps as a clear oil. ^{1}H NMR ($CHCl_3$) 1.40 (m, 2 H), 1.85 (m, 2 H), 2.62 (m, 3 H), 2.97 (m, 3 H), 6.95 (m, 2 H), 7.12 (m, 2 H).

B) **1-[2-(4-Benzyloxyphenoxy)ethyl]-3-(4-fluorobenzyl)pyrrolidine hydrochloride** was prepared from a mixture of 2-(4-benzyloxyphenoxy)ethyl bromide (0.61 g, 2.0 mmol), 3-(4-fluorobenzyl)pyrrolidine (0.36 g, 2.0 mmol), potassium carbonate (0.69 g, 5.0 mmol) in 50 mL of acetonitrile as a white solid (0.35 g, 40%), mp 110-112°C. ^{1}H NMR ($CDCl_3$) 2.02 (m, 2 H), 2.45 (m, 2 H), 2.91 (m, 3 H), 3.42 (m, 2 H), 3.90 (m, 2 H), 4.43 (m, 2 H), 5.02 (s, 2 H), 6.79 (m, 2 H), 6.88 (m, 2 H), 6.98 (m, 2 H), 7.10 (m, 2 H), 7.36 (m, 5 H), 12.90 (brs, 1 H).

Example 38 N-(2-(4-hydroxyphenyl)ethyl)-3-phenylbutylamine

A) N-(2-(4-Hydroxyphenyl)ethyl)-4-phenylbutylamide. 4-Phenylbutyric acid (1.0 g, 6.1 mmol), 1,3-dicyclohexylcarbodiimide (1.27 g, 6.2 mmol), 1-hydroxybenzotriazole (837 mg, 6.2 mmol) and tyramine (849 mg, 6.2 mmol) in DMF (10 mL) was stirred at rt for 3 h then at 80°C for 24 h. The solid was removed by filtration. The solution was diluted with H_2O (150 mL) and the yellow oil was extracted with CH_2Cl_2 (3 x 20 mL). The CH_2Cl_2 extracts were combined and dried over Na_2SO_4 and the solvent was removed in vacuo to give a yellow oil 1.58 g (92 %) as the title compound. ^1H NMR ($CDCl_3$) 1.93 (p, J = 8.1, 2 H). 2.13 (t, J =7.2, 2 H), 2.60 (t, J = 7.8, 2 H), 2.71 (t, J=7.2, 2H), 3.48 (q, J=6.9, 2H), 5.57 (bt, 1H), 6.80 (d, J=6.3, 2H), 7.00 (d, J=8.4, 2H), 7.1-7.4 (m, 5H), 7.99 (s, 1H).

B) N-(2-(4-Hydroxyphenyl)ethyl)-3-phenylbutylamine. $LiAlH_4$ (1.0 g, 26 mmol) was added to freshly distilled THF (100 mL). A solution of N-(2-(4-hydroxyphenyl)ethyl)butylamide (2.0 g, 7.1 mmol) in freshly distilled THF (10 mL) was added slowly to the $LiAlH_4$ suspension with stirring at rt. After addition, the mixture was stirred at rt for 3 h, then was refluxed for 24 h. H_2O (10 mL) was slowly added to the mixture. The resulting precipitate was removed by filtration. The solvent was removed in vacuo. The resulting yellow oil was partitioned between H_2O (25 mL) and CH_2Cl_2 (25 mL). The aqueous phase was separated and was extracted with CH_2Cl_2 (2 x 25 mL). The combined CH_2Cl_2 extract was washed with H_2O (50 mL), dried over Na_2SO_4 and concentrated in vacuo to a white powder. Recrystallization from EtOAc yielded the title compound as a white solid (950 mg, 50%), mp 113-114°C; ^1H NMR ($CDCl_3$) 1.56 (m, 4 H), 2.61 (m, 4 H), 2.73 (t, J = 7.2, 2 H), 2.85 (t, J = 6.9, 2 H), 6.25 (d, J = 8.4, 2 H), 7.02 (d, J = 8.4, 2 H), 7.1-7.3 (m, 5 H).

Example 39 N-(2-(4-hydroxyphenyl)ethyl)-3-phenylpropylamine

A) N-(2-(4-Hydroxyphenyl)ethyl)cinnamide. From cinnamic acid (1.0 g , 6.8 mmol), 1,3-dicyclohexylcarbodiimide (1.42 g, 6.9 mmol), 1-hydroxybenzotriazole (932 mg, 6.9 mmol) and tyramine (945 mg, 6.9 mmol) in DMF (10 mL) was obtained 1.62 g (89%) of the title compound as off-yellow solid, mp 186-187°C, ^{1}H NMR (DMSO-d_6) 1.80 (t, J = 7.5, 2 H), 2.457 (t, 2 H), 2.60 (t, J = 7.8, 2 H), 5.73 (d, J=15.6, 1H), 5.81 (d, J=8.4, 2H), 6.15 (d, J= 15.6, 1H), 6.5-6.7 (m, 5H), 7.30 (t, 1H), 8.33 (s, 1H).

B) N-(2-(4-Hydroxyphenyl)ethyl)-3-phenylpropylamine. N-(2-(4-Hydroxyphenyl)ethyl)cinnamide (1.0 g, 3.7 mmol) was reduced by $LiAlH_4$ (709 mg, 19 mmol) and worked up to give the title compound as a yellow oil (470 mg, 50%) which solidified upon standing. The hydrochloride salt was prepared as a colorless powder quantitatively: ^{1}H NMR ($CDCl_3$) 1.84 (p, J = 7.4, 2 H), 2.59 (t, J = 7.8, 2 H), 2.69 (t, J = 7.2, 2 H), 2.76 (t, J = 6.3, 2 H), 2.89 (t, J = 7.2, 2 H), 6.74 (d, J = 8.4, 2 H), 6.9-7.3 (m, 6 H).

Example 40 N-(2-Phenylethyl)-3-(4-hydroxyphenyl)propylamine

A) N-(2-Phenylethyl)-3-(4-hydroxyphenyl)propylamide. From 3-(4-hydroxyphenyl)propionic acid (1.0 g, 6.0 mmol), 1,3-dicyclohexylcarbodiimide (1.29 g, 6.3 mmol), 1-hydroxybenzotriazole (904 mg , 6.7 mmol) and phenylethylamine (762 mg, 6.3 mmol) in DMF (10 mL) was obtained 1.48 g (92%) of the title compound as off-yellow solid; mp 100-102°C, ^{1}H NMR ($CDCl_3$) 2.39 (t, J = 7.8, 2 H), 2.73 (t, J= 6.9, 2 H), 2.86 (t, J = 7.5, 2 H), 3.47 (q, J=6.3, 2H), 5.20 (s, 1H), 5.50 (s, 1H), 6.77 (d, J=8.1, 2H), 7.04 (d, J=8.4, 2H), 7.10 (d, J= 7.2, 1H), 7.27 (m, 3H).

B) N-(2-Phenylethyl)-3-(4-hydroxyph nyl)propylamine. N-(2-phenylethyl)-(3-(4-hydroxyphenyl)propylamide (1.0 g, 3.7 mmol) was

reduced by $LiAlH_4$ (1.0 g, 26 mmol) and worked up to give the title compound as a yellow oil (800 mg, 84%) which solidified upon standing. The hydrochloride salt was prepared as a colorless powder quantitatively; mp 177-179°C, ^1H NMR ($CDCl_3$) 1.81 (p, J = 7.5, 2 H), 2.54 (t, J = 6.9, 2 H), 2.66 (t, J = 8.1, 2 H), 2.86 (m, 4H), 6.63 (d, J=7.2, 2H), 6.92 (d, J = 8.4, 2 H). 7.3 (m, 5 H).

Example 41 N-(2-(4-Hydroxyphenyl)ethyl)-N-ethyl-4-phenylbutylamine

A mixture of N-(2-(4-hydroxyphenyl)ethyl)-3-phenylbutylamine (200 mg, 0.74 mol), iodoethane (127 mg, 0.81 mmol) and $NaHCO_3$ (68 mg) in CH_3CN was refluxed for 4 h. The solvent was removed and the resulting oil was dissolved in H_2O/CH_2Cl_2 solution (1:1 20 mL). The CH_2Cl_2 layer was removed and the water layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined CH_2Cl_2 layers was dried over Na_2SO_4 and the solvent was removed in vacuo to an off-yellow oil. Column chromatography (twice, EtOAc) resulted in 70 mg (32%) of the title compound as a transparent oil; ^1H NMR ($CDCl_3$) 1.08 (t, J= 7.2, 2H), 1.60 (m, 4 H), 2.50-2.80 (m, 10 H), 5.5 (s, 1H), 6.73 (d, J = 8.4, 2 H), 7.01 (d, J = 8.7, 2 H), 7.1-7.4 (m, 5 H).

Example 42 N-(2-(4-Hydroxyphenyl)ethyl)-(3-butynyl)amine

Tyramine (3.0 g, 22 mmol) and methylsulfonylbut-3-yne (4.3 g, 26 mmol) in acetonitrile (20 mL) was refluxed for 3 h. The solvent was evaporated to an off yellow oil. Column chromatography (hexane, then EtOAc) resulted in 1.8 g (43%) of the title compound which solidified upon standing. ^1H NMR ($CDCl_3$) 1.95 (t, J = 2.7, 1 H), 2.39 (dt, J =2.4,6.6, 2 H), 2.70-3.00 (m, 6 H), 4.2 (s, 2H), 6.74 (d, J=8.1, 2H), 7.06 (d, J=8.1, 2H).

Example 43 N-(2-(4-Hydroxyphenyl)ethyl)-(4-phenyl-3-butynyl)amine

N-(2-(4-Hydroxyphenyl)ethyl)-(3-butynyl)amine (500 mg, 2.6 mmol), iodobenzene (539 mg, 2.6 mmol), $Pd(PPh_3)_2Cl_2$ (19 mg) and CuI (10 mg, 0.052 mmol) in Et_3N (2 mL) was stirred at rt for 3 days. The solvent was removed in vacuo and repetitive column chromatography (EtOAc) followed by preparative TLC (EtOAc) resulted in an off-yellow oil as the title compound (11%); ^1H NMR ($CDCl_3$) 2.63 (t, J=5.1, 4 H), 2.78 (t, J = 5.7, 2 H), 2.80-3.0 (m, 4 H), 4.80 (s, 2H), 6.69 (d, J = 6.7, 2 H), 7.04 (d, J = 7.5, 2 H).

Example 44 N-(2-(4-Hydroxyphenyl)ethyl)-2,5-dichlorocinnamide

The title compound was prepared from 2,5-dichlorocinnamic acid (0.3938 g , 1.815 mmol), $SOCl_2$ (5 mL) and tyramine (0.5478 g , 3.992 mmol), mp 174-175°C, ^1H NMR ($CHCl_3$, 5% DMSO-d_6) 2.47 (t, 2H, J=6.9), 3.20 (q, 2H), 6.70 (d, 1H), 6.46 (d, 2H), 6.73 (d, 2H), 6.95 (d, 2H), 7.05 (d, 2H), 7.55 (d, 1H), 8.45 (s, 1H).

Example 45 N-(2-(4-Hydroxyphenyl)ethyl)-4-chloro-α-cyanocinnamide

A) N-(2-(4-Hydroxyphenyl)ethyl)cyanoacetamide. A mixture of tyramine (5.00 g, 36.5 mmol) and ethyl cyanoacetate (4.10 g , 36.3 mmol) in DMF (50 mL) was stirred at 120°C for 4 h. The mixture was diluted with water (300 mL) and the solution was extracted with ethyl acetate (3 x 100 mL). Combined organic layers were washed with water (100 mL), dried over Na_2SO_4, and the solvent was removed using a rotor evaporator. A yellow solid was obtained. Flash chromatography (CH_2Cl_2/MeOH, 5:1, 50 g silica) yielded 3.48 g (47%) of the title compound. ^1H NMR (DMSO-d_6) 2.55 (t, 2H, J=7.2), 3.18 (t, 2H , J=8.1), 3.54 (s, 1H), 6.62 (d, 2H, J=8.1), 6.94 (d, 2H , J=8.1), 8.225 (s, 1H), 9.16 (s, 1H)

B) N-(2-(4-Hydroxyphenyl)ethyl)-4-chloro-α-cyanocinnamide. A mixture of N-(2-(4-hydroxyphenyl)ethyl)cyanoacetamide (0.600 g, 2.77 mmol), 4-chlorobenzaldehyde (0.600 g, 4.25 mmol) and piperidine (3 drops) in ethanol was refluxed for 3 h. Flash chromatography (CH_2Cl_2/MeOH, 5:1, 40 g silica) followed by two recrystallization from (water/EtOH, 1:1, 80 mL) yielded 0.823 g (60%) of the title compound; mp 170-171°C, ^{1}H NMR (DMSO-d_6) 2.65 (t, 2H, J=7.8), 3.16 (2H), 6.63 (d, 2H , J=8.4), 6.96 (d, 2H , J=8.1), 7.60 (d, 2H , J=8.4), 7.89 (d, 2H , J=8.1), 8.10 (s, 1H), 8.50 (t, 1H), 9.17 (b, 1H).

Example 46 N-(2-(4-Hydroxyphenyl)ethyl)-4-hydroxycinnamide

A mixture of 4-hydroxycinnamic acid (1.00 g, 6.01 mmol), 1,3-dicyclohexylcarbodiimide (0.99 g , 7.32 mmol) and 1-hydroxybenzotriazole (0.99 g , 7.32 mmol) in DMF (25 mL) was stirred at rt for 3 h. Tyramine (1.00 g, 7.32 mmol) was added and the reaction mixture was stirred at 120°C for 12 h. The precipitate was removed by filtration. The solution was diluted with water (300 mL). The solid formed was separated by filtration and dissolved in ethyl acetate (250 mL), washed with acetic acid (2 N in water, 3 x 100 mL), dried over Na_2SO_4, and the volume reduced to 150 mL. The solution was left in the freezer for a period of 24 h which resulted in 1.54 g (89%) of the title compound, mp 247-248°C, ^{1}H NMR (DMSO-d_6) 2.59 (t, 2H , J=7.8), 6.32 (d, 1H , J=15.6), 6.62 (d, 2H , J=8.4), 6.72 (d, 2H, J=8.7), 6.95 (d, 2H , J=8.4), 7.23 (d, 1H, J=15.9), 7.32 (d, 2H, J=8.4), 7.969 (m, 1H), 9.15 (b, 1H), 9.75 (b, 1H).

Example 47 N-(2-(4-Hydroxyphenyl)ethyl)-4-hydroxy-α-cyanocinnamide

The title compound was prepared from N-(2-(4-hydroxyphenyl)-ethyl)-2-cyanoacetamide (0.900 g, 4.17 mmol), 4-hydroxybenzaldehyde (0.610 g, 5.00 mmol) and piperidine (5 drops) in ethanol, mp 209-211°C, ^{1}H NMR (DMSO-d_6)

2.64 (t, 2H, J=7.5), 3.16 (2H), 6.63 (d, 2H, J=8.1), 6.87 (d, 2H, J=8.7), 6.95 (d, 2H, J=8.4), 7.80 (d, 2H, J=8.7), 7.96 (s, 1H), 8.26 (m, 1H), 9.15 (b, 1H).

Example 48 N-(2-(4-Hydroxyphenyl)ethyl)-β-cyanocinnamide

(z)-3-Phenyl-3-cyanopropanoate was dissolved in aqueous HCl (2 N, 100 mL) and extracted with ethyl acetate (3 x 50 mL). The corresponding cinnamic acid obtained (0.87 g, 5.05 mmol) was mixed with 1,3-dicyclohexyl-carbodiimide (1.11 g , 5.40 mmol) and 1-hydroxybenzotriazole (0.76 g, 5.60 mmol) in DMF (25 mL) and was stirred at rt for 3 h. Tyramine (1.15 g, 6.06 mmol) was added and the mixture was stirred at 120°C for 12 h. The precipitate was removed by filtration. The solution was diluted in water (300 mL), and the solid was collected by filtration. Crystallization from ethyl acetate afforded 150 mg (10%) of the title compound. mp 169-171°C, ^{1}H NMR (DMSO-d_6) 2.63 (t, 2H, J=6.0), 3.33 (t, 2H, J=6.0), 6.65 (d, 2H, J=6.9), 7.00 (d, 2H, J=6.9), 7.27 (s, 1H), 7.50 (d, 2H), 7.63 (d, 2H), 8.51 (s, 1H), 9.16 (s, 1H).

Example 49 N-(2-(4-Chlorophenyl)ethyl)-4-hydroxycinnamide

The title compound was prepared from 4-hydroxycinnamic acid (0.80 g, 4.88 mmol), 1,3-dicyclohexylcarbodiimide (1.08 g, 5.22 mmol), 1-hydroxy-benzotriazole (0.85 g, 6.26 mmol) and 2-(4-chlorophenyl)ethylamine (0.92 g, 5.86 mmol) in DMF (20 mL), mp 197-199°C; ^{1}H NMR (DMSO-d_6) 1.90 (t, 2H, J=9.0), 2.55 (t, 2H, J=6.3), 5.54 (d, 1H, J=15.9), 5.94 (d, 2H, J=8.7), 6.2-6.6 (m, 7H), 7.19 (t, 1H), 8.99 (s, 1H).

Example 50 N-(2-(4-chlorophenyl)ethyl)-4-chlorocinnamide

The title compound was prepared from 4-chlorocinnamoyl chloride (500 mg, 3.00 mmol) and 2-(4-chlorophenyl)ethylamine (1.00 g, 7.50 mmol) in DMF (20 mL); mp 171-173°C. ^{1}H NMR (DMSO-d_6) 2.76 (t, 2H , J=7.2), 3.40 (t, 2H, J=7.2), 6.62 (d, 1H, J=15.9), 7.2-7.6 (m, 9H), 8.18 (s, 1H).

Example 51 N-(2-(4-Hydroxyphenyl)ethyl)cinnamide

The title compound was prepared from cinnamoyl chloride (500 mg, 3.00 mmol) and tyramine (1.00 g, 7.50 mmol) in DMF (20 mL); mp 186-187°C; ^{1}H NMR (DMSO-d_6) 1.79 (t, 2H, J=7.5), 2.45 (t, 2H, J=7.5), 5.78 (d, 1H, J=15.6), 5.84 (d, 2H, J=8.4), 6.17 (d, 2H , J=8.1), 6.5-6.6 (m, 4H), 6.71 (d, 2H, J=8.4), 7.30 (t, 1H), 8.33 (s, 1H).

Example 52 2-Phenylethyl 4-Hydroxycinnamate

A mixture of 4-hydroxycinnamic acid (1.8 g. 10 mmol), phenylethyl alcohol (18 mL) and p-toluenesulfonic acid (100 mg) in toluene (100 mL) was refluxed with a Dean-Stark trap for 24 h. Column chromatography ($CHCl_3$/hexane 1:1) yielded 1.48 g (21%) of white solid as the title compound; ^{1}H NMR ($CDCl_3$) 3.02 (t, J = 7.2, 2 H), 4.43 (t, J= 7.2, 2 H), 5.80 (s, 1H), 6.31 (d, J=15.9, 1H), 6.86 (d, J=8.7, 2H), 7.0-7.3 (m, 5H), 7.43 (d, J= 8.7, 2H), 7.65 (d, J=15.9, 1H).

Example 53 In Vitro and In Vivo Assays

Preparation of RNA. cDNA clones encoding the NR1A, NR2A, NR2B, NR2C and NR2D rat NMDA receptor subunits were provided by Dr. P. H. Seeburg (see, Moriyoshi *et al., Nature (Lond.) 354*:31-37 (1991); Kutsuwada *et al., Nature (Lond.) 358*:36-41 (1992); Monyer *et al., Science (Washington, D.C.) 256*:1217-1221 (1992); Ikeda *et al., FEBS Lett. 313*:34-38 (1992); Ishii *et al., J. Biol. Chem. 268*:2836-2843 (1993) for details of these clones or their mouse homologs). The clones were transformed into appropriate host bacteria and plasmid preparations were made with conventional DNA purification techniques. A sample of each clone was linearized by restriction enzyme digestion and cRNA was synthesized with T3 RNA polymerase. The cRNA was diluted to 400 ng/ml and stored in 1 ml aliquots at -80°C until injection.

The Xenopus oocyte expression system. Mature female Xenopus laevis were anaesthetized (20-40 min) using 0.15% 3-aminobenzoic acid ethyl ester (MS-222) and 2-4 ovarian lobes were surgically removed. Oocytes at developmental stages IV-VI (Dumont, J.N., *J. Morphol. 136*:153-180 (1972)), were dissected from the ovary. Oocytes were micro-injected with 1:1 mixtures of cRNA:NR1A + NR2A, 2B, 2C or 2D; injecting ~2, 5, or 20 ng of RNA encoding each receptor subunit. NR1A encoding cRNA was injected alone at ~20 ng. Oocytes were stored in Barth's medium containing (in mM): NaCl, 88; KCl, 1; $CaCl_2$, 0.41; $Ca(NO_3)_2$, 0.33; $MgSO_4$, 0.82; $NaHCO_3$, 2.4; HEPES 5; pH 7.4, with 0.1 mg/ml gentamycin sulphate. Oocytes were defolliculated by treatment with collagenase (0.5 mg/ml Sigma Type I for 0.5-1 hr) (Miledi and Woodward, *J. Physiol. (Lond.) 416*:601-621 (1989)). Electrical recordings were made using a conventional two-electrode voltage clamp (Dagan TEV-200) over periods ranging between 3-14 days following injection. Oocytes were placed in a 0.1 ml recording chamber continuously perfused (5-15 ml min^{-1}) with frog Ringer's solution containing (in mM): NaCl, 115; KCl, 2; $CaCl_2$, 1.8; HEPES, 5;

pH 7.4, or perfused by zero-Ca^{2+}/Ba^{2+} Ringer had the composition (in mM): NaCl. 115; KCl, 2; $BaCl_2$, 1.8; HEPES, 5; pH 7.4. Drugs were applied by bath perfusion. Intraoocyte injections were made by pneumatic pressure-pulse ejection from micropipettes (Miledi and Parker, *J. Physiol. (Lond.) 357*:173-183 (1984)). Injection solutions of EGTA (40-400 mM) and BAPTA (50-500 mM) were made up in H_2O, pH adjusted to 7.4 with KOH or HCl, and filtered to minimize plugging (Acrodisc-13, 0.2 mM). Pressure was set between 200-400 kPa. The volume of injections was regulated by adjusting the time of pulses (0.1-1 sec) and was estimated by measuring the diameters of ejected droplets.

Data Analysis. The logistic equation (equation 1) was fit to the data for individual concentration-response relations by adjusting the slope factor, n, and the parameter pEC_{50}; pEC_{50} = -log EC_{50} where EC_{50} is the agonist concentration that produces half the maximum response (De Lean *et al., Am. J. Physiol. 235*:E97-E102 (1978)) (Origin: Microcal Software).

$$I/I_{max} = 1/(1+(10^{-pEC50}/[agonist])^n) \qquad \text{Eq. 1}$$

Concentration-inhibition curves were fit with equation 2:

$$I/I_{control} = 1/(1+([antagonist]/10^{-pIC_{50}})^n) \qquad \text{Eq. 2}$$

in which $I_{control}$ is the current evoked by agonists alone, pIC_{50} = -log IC_{50}, IC_{50} is the concentration of antagonist that produces half maximal inhibition, and n is the slope factor. For incomplete curves analysis by fitting was unreliable and IC_{50} values were calculated by simple regression over linear portions of the curves (Origin: Microcal Software).

Drugs. The drugs were synthesized as described in the Examples above).

Drugs were initially dissolved at concentrations of 10-100 mM in DMSO. Dilutions were then made to generate a series of DMSO stock solutions over the range 10 mM to 100 mM. Working solutions were made by 1000-3000 fold dilution of stocks into Ringer. At these dilutions DMSO alone had no measurable effects on membrane current responses. DMSO stock solutions were stored for up to two weeks in the dark at 4°C without apparent reductions in potency. Ringer solutions of drugs were made up fresh each day of use.

The MES test for anticonvulsant activity was carried out as described infra.

The alpha1 adrenoreceptor binding assay was carried out as described in Japan *J. Pharmacol. 56*:523-530 (1991). On the day of the assay, previously prepared membranes were thawed and 60 mM Tris-HCl (pH 7.4) was added to yield a final protein concentration of 0.4 mg/ml.

The membrane suspension was incubated for 45 min at room temperature in a total vol of 1ml with [^{3}H]-prazosin (final concentration 1.6 nM). At the end of the incubation period, the incubation medium was immediately filtered through a GF/C glass fiber using a Brandel Cell Harvester followed by three, 3 ml washes with ice-cold buffer. The filters were transferred to scintillation vials and 5 ml of scintillation cocktail was added, vials were shaken overnight and the radioactivity was counted by liquid scintillation spectroscopy. The specific binding was determined by subtracting the non-specific binding in the presence of 10 uM phentolamine from the total.

Inhibition dose response curves were performed using increasing concentration of various compounds (5 nM-100 uM).

Results

The results from the various assays are shown in Table 1.

TABLE 1

Compound name or Ex. #	2A	2B	2C	MES ED_{50}	Alphal
Nylidrin hydrochloride	13	0.23	50	5	5
Isoxsuprine	50	0.8	>100		1
N-[2-(4-hydroxyphenyl)ethyl]-N-(1,2,3,4-tetrahydronaphthylene-1-one-2-yl-methyl)-amine hydrochloride	35	1.3	>300		0.5
N-ethyl-N-(2-phenylethyl)-5-hydroxy-1,2,3,4-tetrahydronaphthylene-2-amine hydrochloride	10	2	30		
N-[2-(3,4-dihydroxyphenyl)ethyl)]-1-(4-hydroxyphenyl)-3-butylamine hydrochloride	30	5	100		
N-[(2-phenyl)ethyl]-3-phenylpropylamine	100	6	>100		1.7
N-[(1-phenyl)-2-propyl]-3-phenylpropyl-1-amine hydrochloride	30	10	100		
N-[1-((3-trifluoromethyl)phenyl)-2-propyl]-3-phenylpropyl-1-amine hydrochloride	20	10	50		
N-{(1-phenyl-1-hydroxy)-2-propyl}-3-phenylpropyl-1-amine hydrochloride	100	12	>100		
Bis-N,N-[2-(4-fluorophenoxy)ethyl]-N-[2-(4-chlorophenyl)ethyl]amine	110	14	>300		
N-[1-(3-methoxyphenyl)-2-propyl]-N-(2-(3-methoxyphenyl)ethyl)amine		16			
4-chloro-N-[2-(4-hydroxyphenyl)ethyl]-cinnamide	240	0.08	250		>250
α-cyano-3,4-dihydroxy-N-(4-phenylbutyl)-cinnamide	80	0.1	100		250
N-(4-phenylbutyl)-4-hydroxycinnamide		0.15	>100		
α-cyano-4-hydroxy-N-(4-phenylbutyl)-cinnamide	>300	0.2	>300		
α-cyano-3,4-dihydroxy-N-(2-phenylethyl)-cinnamide	200	1	200		
N-(4-phenylbutyl)-3,4-dihydroxycinnamide	>300	20	>300		
N-(4-phenylbutyl)cinnamide	120	20	>300		

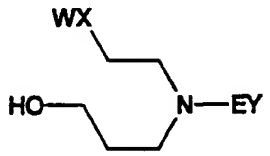
Compound name or Ex. #	2A	2B	2C	MES ED_{50}	Alphal
4-chloro-N-(3-hydroxypropyl)cinnamide	>300	35	>300		
α-cyano-N-(4-phenylbutyl)cinnamide	>300	80	>300		
α-cyano-4-fluoro-N-(4-phenylbutyl)-cinnamide	280	150	>300		
α-cyano-3-hydroxy-N-(4-phenylbutyl)-cinnamide	>300	>300	>300		
4-chloro-α-cyano-N-(4-phenylbutyl)-cinnamide	260	240	>300		
α-cyano-3,4-dihydroxy-N-(4-phenylbutyl)-cinnamide	80	0.1	100		250
α-cyano-3,4-dihydroxy-N-(3-phenyl-propyl)cinnamide	200	0.3	200		>250
α-cyano-3,4-dihydroxy-N-(2-phenylethyl)-cinnamide	200	1	200		
2-(2-thienyl)ethyl-α-cyano-3,4-dihydroxy-cinnamate	160	2	130		>250
α-cyano-3,4-dihydroxy-N-phenylcinnamide	>300	22	>300		
N-(α-cyano-3,4-dihydroxystyryl)-2,3-di-hydroindole amide	120	33	260		
(S)-α-cyano-3,4-dihydroxy-N-(1-phenyl-ethyl)cinnamide	>300	40	260		
(R)-α-cyano-3,4-dihydroxy-N-(1-phenyl-ethyl)cinnamide	>300	55	220		
3,4-dihydroxycinnamic acid	>300	280	>300		
α-cyano-3,4-dihydroxycinnamide	>300	>300	>300		
4-(4-chlorophenyl)-4-hydroxy-1-(4-(4-fluorophenyl)butanoyl-piperidine	100	100	100		
4'-benzylpiperidinyl-4-hydroxycinnamide	230	0.3	>300		
N-(4-phenylbutyl)-3-(4-hydroxyphenyl)-propionamide	>300	0.1	>300		
Ex. 29	45	14	70		
Ex. 30	38	0.2	140	4.0	0.6
Ex. 31	55	10	30		

Compound name or Ex. #	2A	2B	2C	MES ED_{50}	Alpha1
Ex. 32	7.5	0.11	120		
Ex. 33	55	2.3	60		
Ex. 34	90	0.1	95		
Ex. 36		0.12	85	4.0	
Ex. 38	15	0.04	56	2	0.49
Ex. 39	30	0.12	190	2.5	0.50
Ex. 40	48	0.71	240		
Ex. 41	24	0.35	84		
Ex. 43	11	0.17	15		
Ex. 44	>300	16	120		
Ex. 45	>300	11	250		
Ex. 46	>300	20	200		
Ex. 47	280	42	160		
Ex. 48	>300	54	280		
Ex. 49	100	0.16	>300		
Ex. 52	21	15	230		

Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What Is Claimed Is:

1. A compound having the Formula (*VIII*):



(VIII)

or a pharmaceutically acceptable salt thereof;wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, carbonyl, oxygen, or NR;

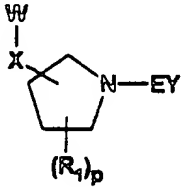
E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, ≡-Y_1, =-Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl; and

R is hydrogen, alkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl;with the proviso that neither W nor Y is p-hydroxyphenyl.

2. A compound having the Formula (*IX*):



(IX)

or a pharmaceutically acceptable salt thereof;

wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, carbonyl, oxygen, sulfur, or NR;

E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r. s and t is other than 0;

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, ≡-Y_1, =-Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino;

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, optionally substituted cycloalkyl, an

aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, an optionally substituted aryl group, an optionally substituted aralkyl group, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, a heteroaryl group, a heteroaryl substituted alkyl group, a fused cycloalkyl group, a fused cycloalkyl group which is further fused to an optionally substituted benzene ring, a carboxy group or an alkyl carboxy (ester) group;

m is 0, 1, 2, or 3; and

p is 0, 1 or 2.

3. A compound according to claim 2 wherein X is CH_2.

4. A compound according to claim 2, said compound selected from the group consisting of:

3-(2-fluorobenzyl)-1-(2-(4-hydroxyphenoxy)ethyl)pyrrolidine;

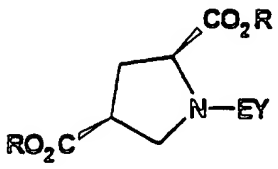
3-(2-fluorobenzyl)-1-(2-(3-fluoro-4-hydroxyphenoxy)ethyl)pyrrolidine;

3-(2-fluorobenzyl)-1-(2-(4-hydroxy-3-methylphenoxy)ethyl)pyrrolidine;

3-(4-fluorobenzyl)-1-(2-(4-hydroxyphenoxy)ethyl)pyrrolidine; and

3-(4-methylbenzyl)-1-(2-(4-hydroxyphenoxy)ethyl)pyrrolidine.

5. A compound having the Formula (X):



(X)

or a pharmaceutically acceptable salt thereof;

wherein

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, $\equiv$-Y_1, $=$-Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino;

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, optionally substituted cycloalkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

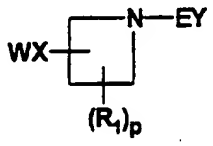
R_1 is hydrogen, hydroxy, an optionally substituted aryl group, an optionally substituted aralkyl group, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, a heteroaryl group, a heteroaryl substituted alkyl group, a fused cycloalkyl group, a fused cycloalkyl group which is further fused to an optionally substituted benzene ring, a carboxy group or an alkyl carboxy (ester) group;

m is 0, 1 or 2;

E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and

s is 0 or 1.

6. A compound having the Formula (*XI*):



(XI)

or a pharmaceutically acceptable salt thereof;

wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, carbonyl, oxygen, or NR;

E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, $\equiv$-Y_1, $=Y_1$, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally

substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino;

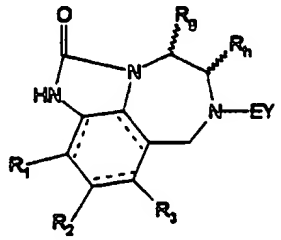
Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl;

R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group; m is 0, 1, 2, or 3; and

p is 0, 1 or 2.

7. A compound having the Formula (*XII*):



(XII)

or a pharmaceutically acceptable salt thereof;

wherein

R_g and R_h are independently hydrogen or alkyl;

R_1-R_3 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

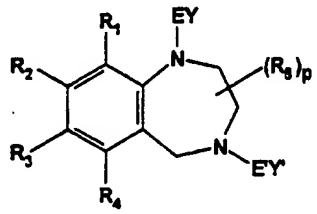
E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_u$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of

hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, $\equiv$-Y_1, =-Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl.

8. A compound having the Formula (*XIII*):



(XIII)

or a pharmaceutically acceptable salt thereof;

wherein

R_1-R_4 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, cyanamido, $N(CN)_2$, guanadino, amidino, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

E and E' are independently $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

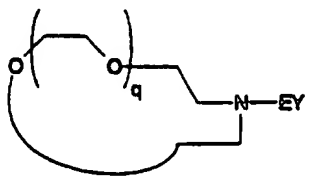
R_5 is hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

p is 0, 1, 2, or 3;

Y and Y' are independently hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, ≡-Y_1, =-Y_1 (which may be cis or trans, throughout) carbonylamido, hydrazino, oximo, amidino, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl.

9. A compound having the Formula (*XIV*):



(*XIV*)

or a pharmaceutically acceptable salt thereof;

wherein

q is 2, 3, 4 or 5;

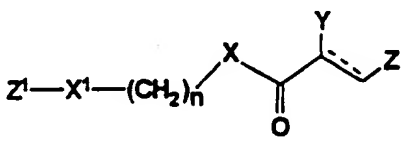
E is $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d may differ with each repetitive methylene and are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

Y is hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, ≡-Y_1, =-Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl.

10. A quaternary ammonium salt of a compound of any one of claims 1-9, obtained by reacting the compound with a lower alkyl halide.

11. A compound having the Formula (*XV*):



or a pharmaceutically acceptable salt thereof;

wherein:

X is NR, O, or CHR^1, wherein R and R^1 are independently hydrogen, alkyl or aralkyl;

X^1 is NR^2, O, S or $(CHR^3)_m$, wherein R^2 and R^3 are independently hydrogen, alkyl or aralkyl and m is 0, 1, 2, 3, 4 or 5;

or where R or R^1 together with R^2 or R^3 is $(CH_2)_p$, wherein p is 0, 1, 2, 3 or 4;

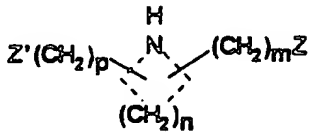
n is 0, 1, 2, 3, 4, 5 or 6;

Z and Z' are independently substituted or unsubstituted aromatic or heteroaromatic groups, adamantyl, hydroxy, or guanidino;

---- can be single or double bond; and

Y is CN or hydrogen.

12. A compound having the Formula (*XVI*):



or a pharmaceutically acceptable salt thereof;

wherein:

n is 0, 1, 2, 3, 4 or 5;

m is 0, 1, 2, 3 or 4;

p = 0, 1, 2, 3 or 4; and

Z and Z' are independently substituted or unsubstituted aromatic or heteroaromatic groups, or adamantyl.

13. A pharmaceutical composition comprising the compound of any one of claims 1-9, 11 and 12 and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition comprising the compound of claim 10 and a pharmaceutically acceptable carrier.

15. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating or preventing aminoglycoside antibiotic-induced hearing loss, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, psychosis, convulsions, chronic pain, migrane headache, glaucoma, CMV retinitis, urinary incontinence or inducing anesthesia, enhancing cognition, treating or preventing opiate tolerance or treating opiate withdrawal, comprising administering to an animal in need of such treatment an effective amount of a compound of any one of claims 1-7, 9 and 10.

16. The method of claim 15, wherein said compound is administered as part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

17. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating or preventing aminoglycoside antibiotic-induced hearing loss, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, psychosis, convulsions, chronic pain, migrane headache, glaucoma, CMV retinitis, urinary incontinence or inducing anesthesia, enhancing cognition, treating or preventing opiate tolerance

or treating opiate withdrawal, comprising administering to an animal in need of such treatment an effective amount of a compound of claim 10.

18. The method of claim 17, wherein said compound is administered as part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

19. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating or preventing aminoglycoside antibiotic-induced hearing loss, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, psychosis, convulsions, chronic pain, migrane headache, glaucoma, CMV retinitis, urinary incontinence or inducing anesthesia, enhancing cognition, treating or preventing opiate tolerance or treating opiate withdrawal, comprising administering to an animal in need of such treatment an effective amount of a compound having the Formula (*VII*):

(VII)

wherein

E and E' are independently $(CR_aR_b)_r$-G_s-$(CR_cR_d)_t$, wherein R_a, R_b, R_c and R_d are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO_2 or O_2C), carbonyl, or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1; with the proviso that at least one of r, s and t is other than 0;

Y and Y' are independently hydrogen, hydroxy, CH_3, CN, CO_2R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted

arylthioxy, optionally substituted aroyl, ≡-Y_1, =-Y_1, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl; and

R is hydrogen, alkyl, or aryl.

20. The method of claim 19, wherein said compound is administered as part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20086

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL : 514/424, 523, 538, 549; 564/282; 548/528; 558/392; 564/182
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/424, 523, 538, 549; 564/282; 548/528; 558/392; 564/182

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online structure

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category°	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,430,044 A (GRIFFITH et al.) 04 July 1995, see entire document.	1, 10, 13-18 (in part)
Y	AU 157,338 A (BURROUGHS WELLCOME & CO. LTD.) 09 August 1951, see formuia i.	2-4, 10, 13-18 (in part)
A	US 4,902,334 A (AZUMA et al.) 20 February 1990, see entire document.	11, 13-18 (in part)

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

°	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date		
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search 25 MARCH 1997	Date of mailing of the international search report 29 MAY 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JACQUELINE HALEY Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)☆

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20086

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-4, 11, 10 (as relates to claims 1-4), 13-18 (as relates to claims 1-4, 11)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20086

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/13, 31/16, 31/215, 31/275, 31/395; C07C 211/08, 233/19, 255/03, 69/612; C07D 207/12

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1, each of 10, 13-18 in part, drawn to compounds of formula VIII.
Group II, claim(s) 2-4, each of 10, 13-18 in part, drawn to compounds of formula IX.
Group III, claim(s) 5, each of 10, 13-18 in part, drawn to compounds of formula X.
Group IV, claim(s) 6, each of 10, 13-18 in part, drawn to compounds of formula XI.
Group V, claim(s) 7, each of 10, 13-18 in part, drawn to compounds of formula XII.
Group VI, claim(s) 8, each of 10, 13-18 in part, drawn to compounds of formula XIII.
Group VII, claim(s) 9, each of 10, 13-18 in part, drawn to compounds of formula XIV.
Group VIII, claim(s) 11, each of 13-18 in part, drawn to compounds of formula XV.
Group IX, claim(s) 12, each of 13-18 in part, drawn to compounds of formula XVI.
Group X, claim(s) 19-20, drawn to methods of using compounds of formula VII.

The inventions listed as Groups I-X do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The groups represent compounds of varying chemical structure. The compounds are so unrelated in structure that a prior art reference anticipating compounds of one group would not even suggest compounds of the other groups.